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Inventor(s):

GILL ADRIAN LIAM [GB]; WOODHEAD STEVEN JOHN [GB]; WOODHEAD ANDREW JAMES [GB]; FREDERICKSON MARTYN [GB]; PADOVA ALESSANDRO [GB]; APAYA ROBERT PATRICK [GB] ;

Applicant(s):

ASTEX TECHNOLOGY LTD [GB];; GILL ADRIAN LIAM [GB];; WOODHEAD STEVEN JOHN [GB];; WOODHEAD ANDREW JAMES [GB];; FREDERICKSON MARTYN [GB];; PADOVA ALESSANDRO [GB];; APAYA ROBERT PATRICK [GB] ;

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ABSTRACT:

The use of a compound of the formula I or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment of a condition ameliorated by the inhibition of raf kinase, wherein: -X=Y- is selected from -CR=CR- and -CR=N-; R is selected from H, halo, NRR', NHC (=O)R, NHC (=O)NRR', NH2SO2R, and C (=O)NRR', where R and R' are independently selected from H and C1-4 alkyl, and are optionally substituted by OH, NH2, SO2-NH2, C5-20 carboaryl, C5-20 heteroaryl and C3-20 heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C5-7 heterocyclyl group; R and R (where present) are independently selected from H, optionally substituted C1-7 alkyl, optionally substituted C5-20 aryl, optionally substituted C3-20 heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino; R an optionally substituted C5-20 carboaryl or C5-20 heteroaryl group; and R is selected from R', halo, NHR, C(=O)NHR, OR', SR, NHC (=O)R, NHC (=O)NHR, NHS (=O) 2R, wherein R is H or C1-3 alkyl (optionally substituted by halo, NH2, OH, SH).

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(71) Applicant *(for all designated States except US)*: **ASTEX TECHNOLOGY LIMITED** [GB/GB]; 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **GILL, Adrian, Liam** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB). **WOODHEAD, Steven, John** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB). **WOODHEAD, Andrew, James** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB). **FREDERICKSON, Martyn** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB). **PADOVA, Alessandro** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB). **APAYA, Robert, Patrick** [GB/GB]; Astex Technology Limited, 436 Cambridge Science Park, Milton Road, Cambridge Cambridgeshire CB4 0QA (GB).

(74) Agents: **WATSON, Robert** et al.; Mewburn Ellis LLP, York House, 23 Kingsway, London Greater London WC2B 6HP (GB).

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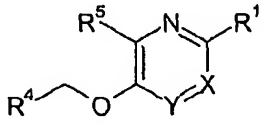

(I)

(57) **Abstract:** The use of a compound of the formula I or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment of a condition ameliorated by the inhibition of raf kinase, wherein: -X=Y- is selected from $-CR^2=CR^3-$ and $-CR^2=N-$; R^1 is selected from H, halo, NRR', NHC (=O)R, NHC (=O)NRR', NH_2SO_2R, and C (=O)NRR', where R and R' are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, SO_2-NH_2, C_{5-20} carboaryl, C_{5-20} heteroaryl and C_{3-20} heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group; R^2 and R^3 (where present) are independently selected from H, optionally substituted C_{1-7} alkyl, optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino; R^4 an optionally substituted C_{5-20} carboaryl or C_{5-20} heteroaryl group; and R^5 is selected from $R^{5'}$, halo, $NHR^{5'}$, $C(=O)NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, NHC (=O)$R^{5'}$, NHC (=O)$NHR^{5'}$, NHS (=O)$_2R^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl (optionally substituted by halo, NH_2, OH, SH).

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raf Kinase Inhibitors

This invention relates to pyridine and pyrazine derivatives which inhibit the activity of raf kinase, and the use of these compounds as pharmaceuticals.

Background

Raf kinase is key downstream target for the ras GTPase and mediates the activation of the MAP kinase cascade consisting of raf-MEK-ERK. Activated ERK is a kinase that subsequently targets a number of proteins responsible for mediating amongst other things the growth, survival and transcriptional functions of the pathway. These include the transcription factors ELK1, C-JUN, Ets 7 and the FOS family. The ras-raf-MEK-ERK signal transduction pathway is activated in response to many cell stimuli including growth factors such as EGF, PDGF, KGF etc. Because the pathway is a major target for growth factor action the activity of raf-MEK-ERK has been found to be upregulated in many factor dependent tumours. The observation that about 20% of all tumours have undergone an activating mutation in one of the ras proteins indicates that the pathway is more broadly important in tumorigenesis. There is growing evidence that activating mutations in other components of the pathway also occur in human tumours. This is true for the raf kinases.

There are 3 closely related isoforms of raf, (A-raf, B-raf, and c-raf-1) which are activated by ras and translocate to the membrane as a consequence of this interaction. Recent evidence indicates that mutational activation of B-raf is found in a number of different tumours including >65% of malignant melanomas , >10% of colorectal cancers (Rajagopalan, H. *et al.*, *Nature*, **418**, 934(2002)), ovarian cancers (Singer, G., *et al.*, *J. Natl. Cancer Inst.*, **95**, 484-486 (2003)) and papillary thyroid cancers (Brose, M., *et al.*, *Cancer Res.*, **62**, 6997-7000(2002); Cohen, Y., *et al.*, *Invest. Ophthalmol. Vis. Sci.*, **44**, 2876-2878(2003)). A range of different B-raf mutations have been identified in different tumours with the most common being a V599E mutation in

the so-called activation loop of the kinase domain (Davies, H., *et al.*, *Nature*, **417**, 949-954 (2002).

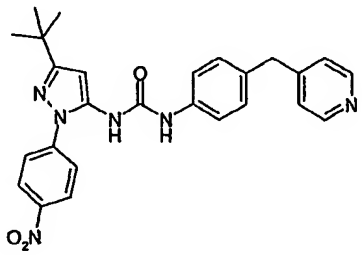
Other mutations of B-raf found associated with human cancers may not necessarily activate B-raf kinase directly but do up-regulate the activity of the ras-raf-MEK-ERK pathway by mechanisms which are not fully understood but may involve cross talk with other raf isoforms, such as A-raf (Wan, P., *et al.*, *Cell*, **116**, 855-867 (2004)). In such cases inhibition of raf activity would remain a beneficial aim in cancer treatment.

In addition to link between B-raf and certain tumour types, there is a significant amount of evidence to indicate a more broad inhibition of raf kinase activity could be beneficial as an antitumour therapy. Blocking the pathway at the level of B-raf would be effective at counteracting the upregulation of this pathway caused by tumourigenic ras mutations and also in tumours responding to growth factor action via this pathway. Genetic evidence in Drosophila and C. elegans indicates that raf homologues are essential for ras dependent actions on differentiation (Dickson, B., *et al.*, *Nature*, **360**, 600-603 (1993)). Introduction of constitutively active MEK into NIH3T3 cells can have a transforming action whilst expression of dominant negative MEK proteins can suppress the tumourigenicity of ras transformed cell lines (Mansour, S.J., *et al.*, *Science*, **265**, 966-970 (1994); Cowely, S., *et al.*, *Cell*, **77**, 841-852 (1994)). Expression of a dominant negative raf protein has also been found to inhibit ras dependent signalling as has suppression of raf expression using an antisense oligonucleotide construct (Koch, W., *et al.*, *Nature*, **349**, 426-428 (1991); Bruder, T.T., *et al.*, *Genes and Development*, **6**, 545-556 (1992))

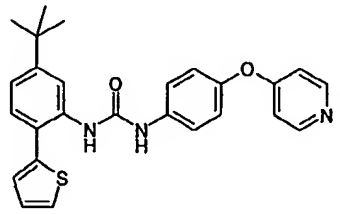
Therefore evidence suggests that inhibition of raf kinase activity could be beneficial in the treatment of cancer and that targeting inhibition of B-raf could be particularly beneficial in those cancers containing a constitutively activated B-raf mutation.

The raf-MEK-ERK pathway functions downstream of many receptors and stimuli indicating a broad role in regulation of cell function. For this reason inhibitors of raf may find utility in other disease conditions which are associated with upregulation of signalling via this pathway. The raf-MEK-ERK pathway is also an important component of the normal response of non-transformed cells to growth factor action. Therefore inhibitors of raf may be of use in diseases where there is inappropriate or excessive proliferation of normal tissues. These include, but are not limited to glomerulonephritis and psoriasis.

Bayer have disclosed series of compounds which act as raf kinase inhibitors; one such compound (WO 99/32455) has the structure:



Another such compound (WO 99/32436) has the structure:

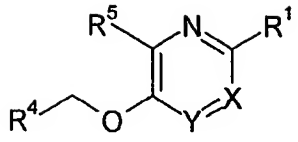


All references cited are incorporated herein by reference.

Summary of the Invention

The present inventors have discovered that pyridine and pyrazine derivatives can be used as pharmaceuticals to inhibit the activity of raf kinase.

Accordingly, the first aspect of the present invention provides the use of a compound of formula I:



or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment or prevention of a disease or condition ameliorated by the inhibition of raf kinase,

wherein:

-X=Y- is selected from $-CR^2=CR^3-$ and $-CR^2=N-$;

R^1 is selected from H, halo, NRR', NHC(=O)R, NHC(=O)NRR', NH_2SO_2R, and C(=O)NRR', where R and R' are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, SO_2-NH_2, C_{5-20} carboaryl, C_{5-20} heteroaryl and C_{3-20} heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group;

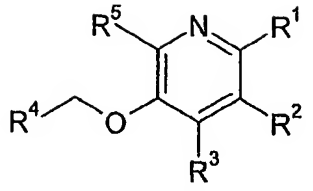
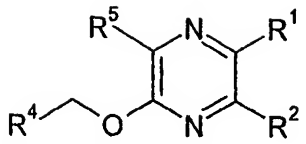
R^2 and R^3 (where present) are independently selected from H, optionally substituted C_{1-7} alkyl, optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino;

R^4 an optionally substituted C_{5-20} carboaryl or C_{5-20} heteroaryl group; and

R^5 is selected from $R^{5'}$, halo, $NHR^{5'}$, $C(=O)NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, $NHC(=O)R^{5'}$, $NHC(=O)NHR^{5'}$, $NHS(=O)_2R^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl (optionally substituted by halo, NH_2, OH, SH).

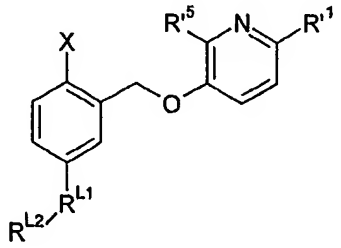
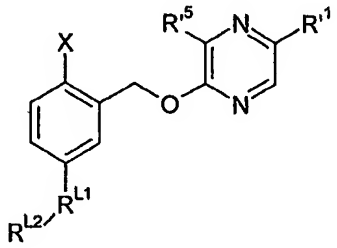
The above aspect may relate to the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a disease or condition ameliorated by the inhibition of raf kinase.

The two possibilities for -X=Y- result in compounds of formulae **Ia** and **Ib**:

where R^1, R^2, R^3, R^4 and R^5 are as defined above.

Particularly preferred compounds of the present invention are of formulae **IIa** and **IIb**:

(IIa) (IIb)

wherein:

R'^1 is selected from H, $NR^{C1}R^{C2}$, $NHC(=O)R^{C1}$, $NHC(=O)NR^{C1}R^{C2}$, $NH_2SO_2R^{C1}$, and $C(=O)NR^{C1}R^{C2}$, where R^{C1} and R^{C2} are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, C_{5-20} carboaryl, and C_{5-20} heteroaryl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group;

R'^5 is selected from H and NH_2;

X is selected from H and halo;

R^{L1} is selected from -NH-C(=O)-, -NH-C(=O)-NH-, -NH-C(=O)-O- or -O-C(=O)-NH-;

R^{L2} is selected from H, optionally substituted C_{5-20} carboaryl and optionally substituted C_{5-20} heteroaryl, except that R^{L2} cannot be H when R^{L1} is -NH-C(=O)-O-.

Diseases or conditions ameliorated by the inhibition of raf kinase are discussed herein, and include, but are not limited to cancer.

Proliferative diseases, including cancers, may be treated or prevented by the inhibition of raf kinase. As discussed below,

the compounds of the present invention may find particular use in the treatment of diseases, for example, cancers, with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals;

(d) upregulation of growth factor receptors, such as ERB2 and EGFR.

Thus, a second aspect of the present invention provide the use of a compound of the first aspect of the invention for the manufacture of a medicament for use in the treatment and/or prophylaxis of cancer. This aspect may also relate to the use of a compound of the first aspect of the invention for the manufacture of a medicament for use in alleviating and/or reducing the incidence of cancer.

Preferably, the cancers treated are those with elevated level of raf kinase, particularly B-raf kinase.

A third aspect of the invention provides a method of inhibiting raf kinase *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound of the first aspect of the invention.

A fourth aspect of the invention pertains to a method for the treatment of a disease or condition ameliorated by the inhibition of raf kinase comprising administering to a subject suffering from said disease or condition ameliorated by the inhibition of raf kinase a therapeutically-effective amount of a compound of the first aspect of the invention.

A fifth aspect of the invention pertains to a method for the treatment of diseases, for example cancers, with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals; or

(d) upregulation of growth factor receptors, such as ERB2 and EGFR, comprising:

(i) diagnosing a subject suffering from a disease with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals; or

(d) upregulation of growth factor receptors, such as ERB2 and EGFR;

(ii) administering to said subject a therapeutically-effective amount of a raf kinase inhibitor of the first aspect of the invention.

In some embodiments, it is preferred that the compounds of the invention selectively inhibit B-raf kinase over at least one other raf kinase (A-raf and/or C-raf-1).

In other embodiments , it is preferred that the treatment is related to or directed at a mutated form of raf, in particular B-raf, such as the mutations discussed in Wan, P., *et al.*, *Cell*, **116**, 855-867 (2004) and WO 03/056036.

Tumours with, for example, activating mutations of ras, raf and EGFR or over expression of ras, raf and EGFR including any of the isoforms thereof, may be particularly sensitive to raf inhibitors.

The compounds of the present invention may be used in the treatment of the cancers described herein, independent of the mechnanisms discussed herein.

The function of inflammatory cells is controlled by many factors the effects of which are mediated by different signal trnsduction pathways. Although some key pro-inflammatory functions are mediated by p38 Map kinase (e.g. TNF release) other are mediated by other pathways. The raf-MEK-ERK pathway in particular is an important activating and proloiferative signal in many inflammatory cells. B and T lymphocytyes in particular require activation of the raf-mek-erk for clonal expansion and generation of effector populations (Cantrell, D.A., *Immunol Rev.*, **192**, 122-30 (2003); Genot, E. and Cantrell, D.A., *Curr Opin Immunol.*, **12(3)**,289-94 (2000)).

Accordingly, the raf kinase inhibitors of formula I may be used in the treatment of inflammatory diseases, such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, and other arthritic conditions; Alzheimer's disease; toxic shock syndrome, the inflammatory reaction induced by endotoxin or inflammatory bowel disease; tuberculosis, atherosclerosis, muscle degeneration, Reiter's syndrome, gout, acute synovitis, sepsis, septic shock, endotoxic shock, gram negative sepsis, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury , graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia, in particular cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), asthma, pulmonary fibrosis and bacterial pneumonia.

Preferred inflammatory disease to be treated include arthritic conditions, including rheumatoid arthritis and rheumatoid spondylitis; inflammatory bowel disease, including Crohn's disease and ulcerative colitis; and chronic obstructive pulmonary disease (COPD).

Definitions

Upregulation of a kinase, includes elevated expression or over-expression of the kinase, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation of the kinase, including activation by mutations.

The phrase "optionally substituted," as used herein, pertains to a parent group which may be unsubstituted or which may be substituted.

Unless otherwise specified, the term "substituted," as used herein, pertains to a parent group which bears one or more substituents. The term "substituent" is used herein in the conventional sense and refers to a chemical moiety which is covalently attached to, appended to, or if appropriate, fused to, a parent group. A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known.

The substituents, and groups listed above, are described in more detail below.

C_{1-7} alkyl: The term "C_{1-7} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 7 carbon atoms, which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "alkyl" includes the sub-classes alkenyl, alkynyl, cycloalkyl, etc., discussed below.

Examples of saturated alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), propyl (C_3), butyl (C_4), pentyl (C_5), hexyl (C_6) and heptyl (C_7).

Examples of saturated linear alkyl groups include, but are not limited to, methyl (C_1), ethyl (C_2), n-propyl (C_3), n-butyl (C_4), n-pentyl (amyl) (C_5), n-hexyl (C_6), and n-heptyl (C_7).

Examples of saturated branched alkyl groups include iso-propyl (C_3), iso-butyl (C_4), sec-butyl (C_4), tert-butyl (C_4), iso-pentyl (C_5), and neo-pentyl (C_5).

C_{3-7} Cycloalkyl: The term "C_{3-7} cycloalkyl" as used herein, pertains to an alkyl group which is also a cyclyl group; that is, a monovalent moiety obtained by removing a hydrogen atom from an alicyclic ring atom of a cyclic hydrocarbon (carbocyclic) compound, which moiety has from 3 to 7 ring atoms. Preferably, each ring has from 3 to 7 ring atoms:

Examples of saturated cylcoalkyl groups include, but are not limited to, those derived from: cyclopropane (C_3), cyclobutane (C_4), cyclopentane (C_5), cyclohexane (C_6) and cycloheptane (C_7).

C_{2-7} Alkenyl: The term "C_{2-7} alkenyl" as used herein, pertains to an alkyl group having one or more carbon-carbon double bonds.

Examples of unsaturated alkenyl groups include, but are not limited to, ethenyl (vinyl, $-CH=CH_2$), 1-propenyl ($-CH=CH-CH_3$), 2-propenyl (allyl, $-CH-CH=CH_2$), isopropenyl ($-C(CH_3)=CH_2$), butenyl (C_4), pentenyl (C_5), and hexenyl (C_6).

Examples of unsaturated cyclic alkenyl groups, which are also referred to herein as "cycloalkenyl" groups, include, but are not limited to, cyclopropenyl (C_3), cyclobutenyl (C_4), cyclopentenyl (C_5), and cyclohexenyl (C_6).

C_{2-7} Alkynyl: The term "C_{2-7} alkynyl", as used herein, pertains to an alkyl group having one or more carbon-carbon triple bonds.

Examples of unsaturated alkynyl groups include, but are not limited to, ethynyl (ethinyl, $-C\equiv CH$) and 2-propynyl (propargyl, $-CH_2-C\equiv CH$).

C_{1-4} alkyl: The term "C_{1-4} alkyl", as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a carbon atom of a hydrocarbon compound having from 1 to 4 carbon atoms, which may be aliphatic or alicyclic, and which may be saturated, partially unsaturated, or fully unsaturated. Thus, the term "C_{1-4} alkyl" includes the sub-classes "C_{2-4} alkenyl", "C_{2-4} alkynyl" and "C_{2-4} cycloalkyl". Examples of these moieties are given above.

C_{3-20} Heterocyclyl: The term "C_{3-20} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 3 to 20 ring atoms, of which from 1 to 10 are ring heteroatoms. Preferably, each ring has from 3 to 7 ring atoms,

of which from 1 to 4 are ring heteroatoms, which include N, O and S.

Examples of monocyclic heterocyclyl groups include, but are not limited to, those derived from:

N_1: aziridine (C_3), azetidine (C_4), pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

O_1: oxirane (C_3), oxetane (C_4), oxolane (tetrahydrofuran) (C_5), oxole (dihydrofuran) (C_5), oxane (tetrahydropyran) (C_6), dihydropyran (C_6), pyran (C_6), oxepin (C_7);

S_1: thiirane (C_3), thietane (C_4), thiolane (tetrahydrothiophene) (C_5), thiane (tetrahydrothiopyran) (C_6), thiepane (C_7);

O_2: dioxolane (C_5), dioxane (C_6), and dioxepane (C_7);

O_3: trioxane (C_6);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6);

O_1S_1: oxathiole (C_5) and oxathiane (thioxane) (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

Nitrogen containing C_{5-7} heterocyclyl: The term "nitrogen containing C_{5-7} heterocyclyl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from a ring atom of a heterocyclic compound, which moiety has from 5 to 7 ring atoms, of which a least one is a nitrogen ring atom. Examples of nitrogen containing C_{5-7} heterocyclyl groups include, but are not limited to, those derived from:

N_1: pyrrolidine (tetrahydropyrrole) (C_5), pyrroline (e.g., 3-pyrroline, 2,5-dihydropyrrole) (C_5), 2H-pyrrole or 3H-pyrrole (isopyrrole, isoazole) (C_5), piperidine (C_6), dihydropyridine (C_6), tetrahydropyridine (C_6), azepine (C_7);

N_2: imidazolidine (C_5), pyrazolidine (diazolidine) (C_5), imidazoline (C_5), pyrazoline (dihydropyrazole) (C_5), piperazine (C_6);

N_1O_1: tetrahydrooxazole (C_5), dihydrooxazole (C_5), tetrahydroisoxazole (C_5), dihydroisoxazole (C_5), morpholine (C_6), tetrahydrooxazine (C_6), dihydrooxazine (C_6), oxazine (C_6);

N_1S_1: thiazoline (C_5), thiazolidine (C_5), thiomorpholine (C_6);

N_2O_1: oxadiazine (C_6); and,

$N_1O_1S_1$: oxathiazine (C_6).

C_{5-20} carboaryl: The term "C_{5-20} carboaryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 20 carbon ring atoms. Preferably, each ring has from 5 to 7 ring atoms.

Examples of carboaryl groups include, but are not limited to, those derived from benzene (i.e. phenyl) (C_6), naphthalene (C_{10}), azulene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

Examples of aryl groups which comprise fused rings, at least one of which is an aromatic ring, include, but are not limited to, groups derived from indene (C_9), isoindene (C_9), and fluorene (C_{13}).

C_{5-20} heteroaryl: The term "C_{5-20} heteroaryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 20 ring atoms, which include one or more heteroatoms. Preferably, each ring has from 5 to 7 ring atoms.

Examples of monocyclic heteroaryl groups include, but are not limited to, those derived from:

N_1: pyrrole (azole) (C_5), pyridine (azine) (C_6);

O_1: furan (oxole) (C_5);

S_1: thiophene (thiole) (C_5);

N_1O_1: oxazole (C_5), isoxazole (C_5), isoxazine (C_6);

N_2O_1: oxadiazole (furazan) (C_5);

N_3O_1: oxatriazole (C_5);

N_1S_1: thiazole (C_5), isothiazole (C_5);

N_2: imidazole (1,3-diazole) (C_5), pyrazole (1,2-diazole) (C_5), pyridazine (1,2-diazine) (C_6), pyrimidine (1,3-diazine) (C_6) (e.g., cytosine, thymine, uracil), pyrazine (1,4-diazine) (C_6);

N_3: triazole (C_5), triazine (C_6); and,

N_4: tetrazole (C_5).

Examples of heteroaryl groups which comprise fused rings, include, but are not limited to:

C_9 heteroaryl groups (with 2 fused rings) derived from benzofuran (O_1), isobenzofuran (O_1), indole (N_1), isoindole (N_1), indolizine (N_1), indoline (N_1), isoindoline (N_1), purine (N_4) (e.g., adenine, guanine), benzimidazole (N_2), indazole (N_2), benzoxazole (N_1O_1), benzisoxazole (N_1O_1), benzodioxole (O_2), benzofurazan (N_2O_1), benzotriazole (N_3), benzothiofuran (S_1), benzothiazole (N_1S_1), benzothiadiazole (N_2S);

C_{10} heteroaryl groups (with 2 fused rings) derived from chromene (O_1), isochromene (O_1), chroman (O_1), isochroman (O_1), benzodioxan (O_2), quinoline (N_1), isoquinoline (N_1), quinolizine (N_1), benzoxazine (N_1O_1), benzodiazine (N_2), pyridopyridine (N_2),

quinoxaline (N_2), quinazoline (N_2), cinnoline (N_2), phthalazine (N_2), naphthyridine (N_2), pteridine (N_4);

C_{13} heteroaryl groups (with 3 fused rings) derived from carbazole (N_1), dibenzofuran (O_1), dibenzothiophene (S_1), carboline (N_2), perimidine (N_2), pyridoindole (N_2); and,

C_{14} heteroaryl groups (with 3 fused rings) derived from acridine (N_1), xanthene (O_1), thioxanthene (S_1), oxanthrene (O_2), phenoxathiin (O_1S_1), phenazine (N_2), phenoxazine (N_1O_1), phenothiazine (N_1S_1), thianthrene (S_2), phenanthridine (N_1), phenanthroline (N_2), phenazine (N_2).

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -NH- group may be N-substituted, that is, as -NR-. For example, pyrrole may be N-methyl substituted, to give N-methypyrrole. Examples of N-substitutents include, but are not limited to C_{1-7} alkyl, C_{3-20} heterocyclyl, C_{5-20} carboaryl, C_{5-20} heteroaryl and acyl groups.

Heterocyclic groups (including heteroaryl groups) which have a nitrogen ring atom in the form of an -N= group may be substituted in the form of an N-oxide, that is, as $-N(\rightarrow O)=$ (also denoted $-N^+(\rightarrow O^-)=$). For example, quinoline may be substituted to give quinoline N-oxide; pyridine to give pyridine N-oxide; benzofurazan to give benzofurazan N-oxide (also known as benzofuroxan).

Cyclic groups may additionally bear one or more oxo (=O) groups on ring carbon atoms. Monocyclic examples of such groups include, but are not limited to, those derived from:

C_5: cyclopentanone, cyclopentenone, cyclopentadienone;

C_6: cyclohexanone, cyclohexenone, cyclohexadienone;

O_1: furanone (C_5), pyrone (C_6);

N_1: pyrrolidone (pyrrolidinone) (C_5), piperidinone (piperidone) (C_6), piperidinedione (C_6);

N_2: imidazolidone (imidazolidinone) (C_5), pyrazolone (pyrazolinone) (C_5), piperazinone (C_6), piperazinedione (C_6), pyridazinone (C_6), pyrimidinone (C_6) (e.g., cytosine), pyrimidinedione (C_6) (e.g., thymine, uracil), barbituric acid (C_6);

N_1S_1: thiazolone (C_5), isothiazolone (C_5);

N_1O_1: oxazolinone (C_5).

Polycyclic examples of such groups include, but are not limited to, those derived from:

C_9: indenedione;

C_{10}: tetralone, decalone;

C_{14}: anthrone, phenanthrone;

N_1: oxindole (C_9);

O_1: benzopyrone (e.g., coumarin, isocoumarin, chromone) (C_{10});

N_1O_1: benzoxazolinone (C_9), benzoxazolinone (C_{10});

N_2: quinazolinedione (C_{10});

N_4: purinone (C_9) (e.g., guanine).

Still more examples of cyclic groups which bear one or more oxo (=O) groups on ring carbon atoms include, but are not limited to, those derived from:

imides (-C(=O)-NR-C(=O)- in a ring), including but not limited to, succinimide (C_5), maleimide (C_5), phthalimide, and glutarimide (C_6);

lactones (cyclic esters, -O-C(=O)- in a ring), including, but not limited to, β-propiolactone, γ-butyrolactone, δ-valerolactone (2-piperidone), and ε-caprolactone;

lactams (cyclic amides, -NR-C(=O)- in a ring), including, but not limited to, β-propiolactam (C_4), γ-butyrolactam (2-pyrrolidone) (C_5), δ-valerolactam (C_6), and ε-caprolactam (C_7);

cyclic carbamates (-O-C(=O)-NR- in a ring), such as 2-oxazolidone (C_5);

cyclic ureas (-NR-C(=O)-NR- in a ring), such as 2-imidazolidone (C_5) and pyrimidine-2,4-dione (e.g., thymine, uracil) (C_6).

The above alkyl, heterocyclyl, carboaryl and heteroaryl groups, whether alone or part of another substituent, may themselves optionally be substituted with one or more groups selected from themselves and the additional substituents listed below, unless otherwise stated. Carboaryl and heteroaryl groups may also be substituted by alkoxylene groups as defined below.

Halo: -F, -Cl, -Br, and -I.

Hydroxy: -OH.

Ether: -OR, wherein R is an ether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7} alkoxy group, discussed below), a C_{3-20} heterocyclyl group (also referred to as a C_{3-20} heterocyclyloxy group), or a C_{5-20} aryl group (also referred to as a C_{5-20} aryloxy group), preferably a C_{1-7} alkyl group. The term C_{5-20} aryl group encompasses both C_{5-20} carboaryl and C_{5-20} heteroaryl groups.

C_{1-7} alkoxy: -OR, wherein R is a C_{1-7} alkyl group. Examples of C_{1-7} alkoxy groups include, but are not limited to, -OMe (methoxy), -OEt (ethoxy), -O(nPr) (n-propoxy), -O(iPr) (isopropoxy), -O(nBu) (n-butoxy), -O(sBu) (sec-butoxy), -O(iBu) (isobutoxy), and -O(tBu) (tert-butoxy).

Acetal: $-CH(OR^1)(OR^2)$, wherein R^1 and R^2 are independently acetal substituents, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group, or, in the case of a "cyclic" acetal group, R^1 and R^2, taken together with the two oxygen atoms to which they are attached, and the carbon atoms to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Examples of acetal groups include, but are not limited to, $-CH(OMe)_2$, $-CH(OEt)_2$, and -CH(OMe)(OEt).

Hemiacetal: $-CH(OH)(OR^1)$, wherein R^1 is a hemiacetal substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of hemiacetal groups include, but are not limited to, -CH(OH)(OMe) and -CH(OH)(OEt).

Ketal: $-CR(OR^1)(OR^2)$, where R^1 and R^2 are as defined for acetals, and R is a ketal substituent other than hydrogen, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Examples ketal groups include, but

are not limited to, -C(Me)(OMe)$_2$, -C(Me)(OEt)$_2$, -C(Me)(OMe)(OEt), -C(Et)(OMe)$_2$, -C(Et)(OEt)$_2$, and -C(Et)(OMe)(OEt).

Hemiketal: -CR(OH)(OR^1), where R^1 is as defined for hemiacetals, and R is a hemiketal substituent other than hydrogen, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of hemiketal groups include, but are not limited to, -C(Me)(OH)(OMe), -C(Et)(OH)(OMe), -C(Me)(OH)(OEt), and -C(Et)(OH)(OEt).

Oxo (keto, -one): =O.

Thione (thioketone): =S.

Imino (imine): =NR, wherein R is an imino substituent, for example, hydrogen, C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, =NH, =NMe, =NEt, and =NPh.

Formyl (carbaldehyde, carboxaldehyde): -C(=O)H.

Acyl (keto): -C(=O)R, wherein R is an acyl substituent, for example, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylacyl or C_{1-7} alkanoyl), a C_{3-20}heterocyclyl group (also referred to as C_{3-20} heterocyclylacyl), or a C_{5-20} aryl group (also referred to as C_{5-20} arylacyl), preferably a C_{1-7} alkyl group. Examples of acyl groups include, but are not limited to, -C(=O)CH_3 (acetyl), -C(=O)CH_2CH_3 (propionyl), -C(=O)C(CH_3)$_3$ (t-butyryl), and -C(=O)Ph (benzoyl, phenone).

Carboxy (carboxylic acid): -C(=O)OH.

Thiocarboxy (thiocarboxylic acid): -C(=S)SH.

Thiolocarboxy (thiolocarboxylic acid): -C(=O)SH.

Thionocarboxy (thionocarboxylic acid): -C(=S)OH.

Imidic acid: -C(=NH)OH.

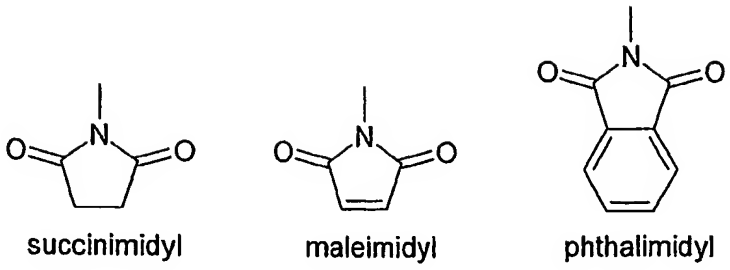
Hydroxamic acid: -C(=O)NHOH.

Ester (carboxylate, carboxylic acid ester, oxycarbonyl): -C(=O)OR, wherein R is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of ester groups include, but are not limited to, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OC(CH_3)_3$, and -C(=O)OPh.

Acyloxy (reverse ester): -OC(=O)R, wherein R is an acyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Examples of acyloxy groups include, but are not limited to, $-OC(=O)CH_3$ (acetoxy), $-OC(=O)CH_2CH_3$, $-OC(=O)C(CH_3)_3$, -OC(=O)Ph, and $-OC(=O)CH_2Ph$.

Amido (carbamoyl, carbamyl, aminocarbonyl, carboxamide): $-C(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-C(=O)NHCH_2CH_3$, and $-C(=O)N(CH_2CH_3)_2$, as well as amido groups in which R^1 and R^2, together with the nitrogen atom to which they are attached, form a heterocyclic structure as in, for example, piperidinocarbonyl, morpholinocarbonyl, thiomorpholinocarbonyl, and piperazinocarbonyl.

Acylamido (acylamino): $-NR^1C(=O)R^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an acyl substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7}alkyl group. Examples of acylamide groups include, but are not limited to, $-NHC(=O)CH_3$, $-NHC(=O)CH_2CH_3$, and -NHC(=O)Ph. R^1 and R^2 may together form a cyclic structure, as in, for example, succinimidyl, maleimidyl, and phthalimidyl:



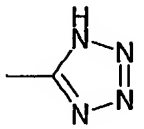
Thioamido (thiocarbamyl): $-C(=S)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of amido groups include, but are not limited to, $-C(=S)NH_2$, $-C(=S)NHCH_3$, $-C(=S)N(CH_3)_2$, and $-C(=S)NHCH_2CH_3$.

Ureido: $-N(R^1)CONR^2R^3$ wherein R^2 and R^3 are independently amino substituents, as defined for amino groups, and R^1 is a ureido substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group. Examples of ureido groups include, but are not limited to, $-NHCONH_2$, $-NHCONHMe$, $-NHCONHEt$, $-NHCONMe_2$, $-NHCONEt_2$, $-NMeCONH_2$, $-NMeCONHMe$, $-NMeCONHEt$, $-NMeCONMe_2$, and $-NMeCONEt_2$.

Carbamate: $-NR^1C(=O)OR^2$, wherein R^1 is an amide substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably hydrogen or a C_{1-7} alkyl group, and R^2 is an ester substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of carbamate groups include, but are not limited to, $-NHC(=O)OCH_3$, $-NHC(=O)OCH_2CH_3$, and $-NHC(=O)OPh$.

Guanidino: $-NH-C(=NH)NH_2$.

Tetrazolyl: a five membered aromatic ring having four nitrogen atoms and one carbon atom,



Amino: $-NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, for example, hydrogen, a C_{1-7} alkyl group (also referred to as C_{1-7} alkylamino or di-C_{1-7} alkylamino), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group, or, in the case of a "cyclic" amino group, R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring having from 4 to 8 ring atoms. Amino groups may be primary ($-NH_2$), secondary ($-NHR^1$), or tertiary ($-NHR^1R^2$), and in cationic form, may be quaternary ($-^+NR^1R^2R^3$). Examples of amino groups include, but are not limited to, $-NH_2$, $-NHCH_3$, $-NHC(CH_3)_2$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, and -NHPh. Examples of cyclic amino groups include, but are not limited to, aziridino, azetidino, pyrrolidino, piperidino, piperazino, morpholino, and thiomorpholino.

Imino: =NR, wherein R is an imino substituent, for example, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7} alkyl group. Examples of imino groups include, but are not limited to, =NH, =NMe, and =NEt.

Amidine (amidino): $-C(=NR)NR_2$, wherein each R is an amidine substituent, for example, hydrogen, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably H or a C_{1-7}alkyl group. Examples of amidine groups include, but are not limited to, $-C(=NH)NH_2$, $-C(=NH)NMe_2$, and $-C(=NMe)NMe_2$.

Nitro: $-NO_2$.

Azido: $-N_3$.

Cyano (nitrile, carbonitrile): -CN.

Cyanato: -OCN.

Sulfhydryl (thiol, mercapto): -SH.

Thioether (sulfide): -SR, wherein R is a thioether substituent, for example, a C_{1-7} alkyl group (also referred to as a C_{1-7}

alkylthio group), a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Examples of C_{1-7} alkylthio groups include, but are not limited to, $-SCH_3$ and $-SCH_2CH_3$.

Sulfine (sulfinyl, sulfoxide): $-S(=O)R$, wherein R is a sulfine substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Examples of sulfine groups include, but are not limited to, $-S(=O)CH_3$ and $-S(=O)CH_2CH_3$.

Sulfone (sulfonyl): $-S(=O)_2R$, wherein R is a sulfone substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group, including, for example, a fluorinated or perfluorinated C_{1-7} alkyl group. Examples of sulfone groups include, but are not limited to, $-S(=O)_2CH_3$ (methanesulfonyl, mesyl), $-S(=O)_2CF_3$ (triflyl), $-S(=O)_2CH_2CH_3$ (esyl), $-S(=O)_2C_4F_9$ (nonaflyl), $-S(=O)_2CH_2CF_3$ (tresyl), $-S(=O)_2CH_2CH_2NH_2$ (tauryl), $-S(=O)_2Ph$ (phenylsulfonyl, besyl), 4-methylphenylsulfonyl (tosyl), 4-chlorophenylsulfonyl (closyl), 4-bromophenylsulfonyl (brosyl), 4-nitrophenyl (nosyl), 2-naphthalenesulfonate (napsyl), and 5-dimethylamino-naphthalen-1-ylsulfonate (dansyl).

Sulfinic acid (sulfino): $-S(=O)OH$, $-SO_2H$.

Sulfonic acid (sulfo): $-S(=O)_2OH$, $-SO_3H$.

Sulfinate (sulfinic acid ester): $-S(=O)OR$; wherein R is a sulfinate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinate groups include, but are not limited to, $-S(=O)OCH_3$ (methoxysulfinyl; methyl sulfinate) and $-S(=O)OCH_2CH_3$ (ethoxysulfinyl; ethyl sulfinate).

Sulfonate (sulfonic acid ester): $-S(=O)_2OR$, wherein R is a sulfonate substituent, for example, a C_{1-7}alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonate groups include, but are not limited

to, $-S(=O)_2OCH_3$ (methoxysulfonyl; methyl sulfonate) and $-S(=O)_2OCH_2CH_3$ (ethoxysulfonyl; ethyl sulfonate).

Sulfinyloxy: $-OS(=O)R$, wherein R is a sulfinyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfinyloxy groups include, but are not limited to, $-OS(=O)CH_3$ and $-OS(=O)CH_2CH_3$.

Sulfonyloxy: $-OS(=O)_2R$, wherein R is a sulfonyloxy substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonyloxy groups include, but are not limited to, $-OS(=O)_2CH_3$ (mesylate) and $-OS(=O)_2CH_2CH_3$ (esylate).

Sulfate: $-OS(=O)_2OR$; wherein R is a sulfate substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfate groups include, but are not limited to, $-OS(=O)_2OCH_3$ and $-SO(=O)_2OCH_2CH_3$.

Sulfamyl (sulfamoyl; sulfinic acid amide; sulfinamide): $-S(=O)NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfamyl groups include, but are not limited to, $-S(=O)NH_2$, $-S(=O)NH(CH_3)$, $-S(=O)N(CH_3)_2$, $-S(=O)NH(CH_2CH_3)$, $-S(=O)N(CH_2CH_3)_2$, and $-S(=O)NHPh$.

Sulfonamido (sulfinamoyl; sulfonic acid amide; sulfonamide): $-S(=O)_2NR^1R^2$, wherein R^1 and R^2 are independently amino substituents, as defined for amino groups. Examples of sulfonamido groups include, but are not limited to, $-S(=O)_2NH_2$, $-S(=O)_2NH(CH_3)$, $-S(=O)_2N(CH_3)_2$, $-S(=O)_2NH(CH_2CH_3)$, $-S(=O)_2N(CH_2CH_3)_2$, and $-S(=O)_2NHPh$.

Sulfamino: $-NR^1S(=O)_2OH$, wherein R^1 is an amino substituent, as defined for amino groups. Examples of sulfamino groups include, but are not limited to, $-NHS(=O)_2OH$ and $-N(CH_3)S(=O)_2OH$.

Sulfonamino: $-NR^1S(=O)_2R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfonamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7} alkyl group. Examples of sulfonamino groups include, but are not limited to, $-NHS(=O)_2CH_3$ and $-N(CH_3)S(=O)_2C_6H_5$.

Sulfinamino: $-NR^1S(=O)R$, wherein R^1 is an amino substituent, as defined for amino groups, and R is a sulfinamino substituent, for example, a C_{1-7} alkyl group, a C_{3-20} heterocyclyl group, or a C_{5-20} aryl group, preferably a C_{1-7}alkyl group. Examples of sulfinamino groups include, but are not limited to, $-NHS(=O)CH_3$ and $-N(CH_3)S(=O)C_6H_5$.

Further groups

Alkoxylene: The term "alkoxylene" as used herein, pertains to a bidentate group which may be a substituent of an aryl group. It bonds to adjacent atoms of the aryl group, and may one or two carbon atoms in the chain between the oxygen atoms, as thus has the structure $-O(CH_2)_nO-$, where n is either 1 or 2. The carbon atoms may bear any of the substituents listed above.

Includes Other Forms

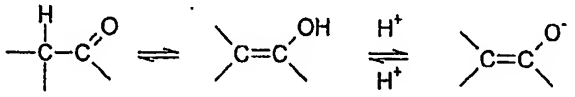
Unless otherwise specified, included in the above are the well known ionic, salt, solvate, and protected forms of these substituents. For example, a reference to carboxylic acid (-COOH) also includes the anionic (carboxylate) form ($-COO^-$), a salt or solvate thereof, as well as conventional protected forms. Similarly, a reference to an amino group includes the protonated form ($-N^+HR^1R^2$), a salt or solvate of the amino group, for example, a hydrochloride salt, as well as conventional protected forms of an amino group. Similarly, a reference to a hydroxyl group also includes the anionic form ($-O^-$), a salt or solvate thereof, as well as conventional protected forms of a hydroxyl group.

Isomers, Salts, Solvates, Protected Forms, and Prodrugs

Certain compounds may exist in one or more particular geometric, optical, enantiomeric, diasteriomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to, cis- and trans-forms; E- and Z-forms; c-, t-, and r-forms; endo- and exo-forms; R-, S-, and meso-forms; D- and L-forms; d- and l-forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α- and β-forms; axial and equatorial forms; boat-, chair-, twist-, envelope-, and halfchair-forms; and combinations thereof, hereinafter collectively referred to as "isomers" (or "isomeric forms").

Note that, except as discussed below for tautomeric forms, specifically excluded from the term "isomers," as used herein, are structural (or constitutional) isomers (i.e., isomers which differ in the connections between atoms rather than merely by the position of atoms in space). For example, a reference to a methoxy group, $-OCH_3$, is not to be construed as a reference to its structural isomer, a hydroxymethyl group, $-CH_2OH$. Similarly, a reference to ortho-chlorophenyl is not to be construed as a reference to its structural isomer, meta-chlorophenyl. However, a reference to a class of structures may well include structurally isomeric forms falling within that class (e.g., C_{1-7}alkyl includes n-propyl and iso-propyl; butyl includes n-, iso-, sec-, and tert-butyl; methoxyphenyl includes ortho-, meta-, and para-methoxyphenyl).

The above exclusion does not pertain to tautomeric forms, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/amidine, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



keto enol enolate

Note that specifically included in the term "isomer" are compounds with one or more isotopic substitutions. For example, H may be in any isotopic form, including ^{1}H, ^{2}H (D), and ^{3}H (T); C may be in any isotopic form, including ^{12}C, ^{13}C, and ^{14}C; O may be in any isotopic form, including ^{16}O and ^{18}O; and the like.

Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including (wholly or partially) racemic and other mixtures thereof. Isomeric forms substantially free, i.e. associated with less than 5%, preferably less than 2%, in particular less than 1%, of the other isomeric form are also envisaged. Methods for the preparation (e.g., asymmetric synthesis) and separation (e.g., fractional crystallisation and chromatographic means) of such isomeric forms are either known in the art or are readily obtained by adapting the methods taught herein, or known methods, in a known manner.

Unless otherwise specified, a reference to a particular compound also includes ionic, salt, solvate, and protected forms of thereof, for example, as discussed below.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," J. Pharm. Sci., Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be $-COO^{-}$), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^{+} and K^{+}, alkaline earth cations such as Ca^{2+} and Mg^{2+}, and other cations such as Al^{3+}. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH_4^{+}) and substituted ammonium ions (e.g., NH_3R^{+}, $NH_2R_2^{+}$, NHR_3^{+}, NR_4^{+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine,

diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $N(CH_3)_4^+$.

If the compound is cationic, or has a functional group which may be cationic (e.g., $-NH_2$ may be $-NH_3^+$), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pamoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of the active compound. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., active compound, salt of active compound) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

It may be convenient or desirable to prepare, purify, and/or handle the active compound in a chemically protected form. The term "chemically protected form" is used herein in the conventional chemical sense and pertains to a compound in which

one or more reactive functional groups are protected from undesirable chemical reactions under specified conditions (e.g., pH, temperature, radiation, solvent, and the like). In practice, well known chemical methods are employed to reversibly render unreactive a functional group, which otherwise would be reactive, under specified conditions. In a chemically protected form, one or more reactive functional groups are in the form of a protected or protecting group (also known as a masked or masking group or a blocked or blocking group). By protecting a reactive functional group, reactions involving other unprotected reactive functional groups can be performed, without affecting the protected group; the protecting group may be removed, usually in a subsequent step, without substantially affecting the remainder of the molecule. See, for example, Protective Groups in Organic Synthesis (T. Green and P. Wuts; 3rd Edition; John Wiley and Sons, 1999).

A wide variety of such "protecting," "blocking," or "masking" methods are widely used and well known in organic synthesis. For example, a compound which has two nonequivalent reactive functional groups, both of which would be reactive under specified conditions, may be derivatized to render one of the functional groups "protected," and therefore unreactive, under the specified conditions; so protected, the compound may be used as a reactant which has effectively only one reactive functional group. After the desired reaction (involving the other functional group) is complete, the protected group may be "deprotected" to return it to its original functionality.

For example, a hydroxy group may be protected as an ether (-OR) or an ester (-OC(=O)R), for example, as: a t-butyl ether; a benzyl, benzhydryl (diphenylmethyl), or trityl (triphenylmethyl) ether; a trimethylsilyl or t-butyldimethylsilyl ether; or an acetyl ester (-OC(=O)CH_3, -OAc).

For example, an aldehyde or ketone group may be protected as an acetal (R-CH$(OR)_2$) or ketal ($R_2C(OR)_2$), respectively, in which the carbonyl group (>C=O) is converted to a diether (>C$(OR)_2$), by reaction with, for example, a primary alcohol. The aldehyde or

ketone group is readily regenerated by hydrolysis using a large excess of water in the presence of acid.

For example, an amine group may be protected, for example, as an amide (-NRCO-R) or a urethane (-NRCO-OR), for example, as: a methyl amide (-NHCO-CH_3); a benzyloxy amide (-NHCO-$OCH_2C_6H_5$, -NH-Cbz); as a t-butoxy amide (-NHCO-$OC(CH_3)_3$, -NH-Boc); a 2-biphenyl-2-propoxy amide (-NHCO-$OC(CH_3)_2C_6H_4C_6H_5$, -NH-Bpoc), as a 9-fluorenylmethoxy amide (-NH-Fmoc), as a 6-nitroveratryloxy amide (-NH-Nvoc), as a 2-trimethylsilylethyloxy amide (-NH-Teoc), as a 2,2,2-trichloroethyloxy amide (-NH-Troc), as an allyloxy amide (-NH-Alloc), as a 2(-phenylsulphonyl)ethyloxy amide (-NH-Psec); or, in suitable cases (e.g., cyclic amines), as a nitroxide radical (>N-O•).

For example, a carboxylic acid group may be protected as an ester for example, as: an C_{1-7} alkyl ester (e.g., a methyl ester; a t-butyl ester); a C_{1-7} haloalkyl ester (e.g., a C_{1-7} trihaloalkyl ester); a triC_{1-7} alkylsilyl-C_{1-7}alkyl ester; or a C_{5-20} aryl-C_{1-7} alkyl ester (e.g., a benzyl ester; a nitrobenzyl ester); or as an amide, for example, as a methyl amide.

For example, a thiol group may be protected as a thioether (-SR), for example, as: a benzyl thioether; an acetamidomethyl ether (-S-$CH_2NHC(=O)CH_3$).

It may be convenient or desirable to prepare, purify, and/or handle the active compound in the form of a prodrug. The term "prodrug," as used herein, pertains to a compound which, when metabolised (e.g., in vivo), yields the desired active compound. Typically, the prodrug is inactive, or less active than the active compound, but may provide advantageous handling, administration, or metabolic properties.

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups

(-C(=O)OH) in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula -C(=O)OR wherein R is:
C_{1-7}alkyl
(e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);
C_{1-7}aminoalkyl
(e.g., aminoethyl; 2-(N,N-diethylamino)ethyl;
2-(4-morpholino)ethyl); and
acyloxy-C_{1-7}alkyl
(e.g., acyloxymethyl;
acyloxyethyl;
pivaloyloxymethyl;
acetoxymethyl;
1-acetoxyethyl;
1-(1-methoxy-1-methyl)ethyl-carbonxyloxyethyl;
1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl;
1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl;
1-cyclohexyl-carbonyloxyethyl;
cyclohexyloxy-carbonyloxymethyl;
1-cyclohexyloxy-carbonyloxyethyl;
(4-tetrahydropyranyloxy) carbonyloxymethyl;
1-(4-tetrahydropyranyloxy)carbonyloxyethyl;
(4-tetrahydropyranyl)carbonyloxymethyl; and
1-(4-tetrahydropyranyl)carbonyloxyethyl).

For example, some prodrugs are N-oxides of the active compound (where the active compound contains an amine group). Where a compounds contains several amine groups, one or more than one nitrogen atom may be oxidised to from an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a nitrogen atom of a nitrogen containing heterocycle.

N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxycarboxylic acid), see for example *Advanced Organic*

Chemistry, by Jerry March, 4th Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* 1977, 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

N-oxides may be reduced *in vivo* to the active compound.

Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

Preferences

The following preferences apply to each aspect of the present invention, and preferred compounds may be different for different aspects. The following preferences for each group may be combined in any way with preferences for other groups.

In some embodiments, it is preferred that the molecular weight of the compound is less than 1000, and more preferably less than 750, although the molecular weight may be less than 700, 650, 600, 550, 525 or even 500.

-X=Y-

It is preferred that -X=Y- is $-CR^2=N-$, i.e. that the compounds are of formula **Ib**.

R^5

R^5 is preferably selected from $R^{5'}$, halo, $NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl (optionally substituted by halo, NH_2, OH, SH). Of these groups, H, $NHR^{5'}$ (more preferably NH_2), OH, SH and halo (more preferably F or Cl) are more preferred, with H and NH_2 being the most preferred. If the compound is a pyridine then preferably R^5 is NH_2, and if the compound is a pyrazine preferably R^5 is H.

R^1

R^1 is preferably selected from H, NRR', NHC(=O)R, NHC(=O)NRR', and NH_2SO_2R, and more preferably from H and NRR', or from H and NH_2. R^1 is most preferably H.

In some embodiments, R^1 is preferably selected from NHC(=O)R, NHC(=O)NRR', and NH_2SO_2R.

R^2 and R^3

R^2 and R^3 (where present) are preferably independently selected from H, halo, amino, hydroxy and thio, and more preferably from H and halo. If only one of R^2 and R^3 is a substituent, then R^2 is the preferred substituent.

R^4

R^4 is preferably an optionally substituted C_{5-10} aryl group, more preferably either a C_{5-10} carboaryl group or a C_{5-10} heteroaryl group having one or two nitrogen ring atoms, for example, naphthyl, phenyl, indole, quinoline, isoquinoline, tetrahydroquinoline, tetrahydroisoquinoline, pyridine, phthalazine, tetrahydrophthalazine, quinazoline and tetrahydroquinazoline.

In one embodiment R^4 is an optionally substituted C_{5-10} carboaryl group, and more preferably an optionally substituted phenyl or napthyl group.

If R^4 is a napthyl group it is preferably unsubstituted, and may be in any configuration, with napth-1-yl being preferred.

If R^4 is a phenyl group, then it is preferably substituted, more preferably with one or two substituents.

These are preferably selected from halo (more preferably F and Cl), ether (more preferably C_{1-7} alkoxy, and in particular -OMe, and arylalkoxy, and in particular benzyloxy), C_{1-7} alkyl (more preferably C_{1-4} alkyl, and in particular -Me, and $-CF_3$), C_{5-20} aryl

groups (more preferably C_{5-10} carboaryl or heteroaryl groups), amido, acylamido, ureido, carbamate and reverse carbamate. Alkoxylene groups linked to adjacent atoms are also preferred.

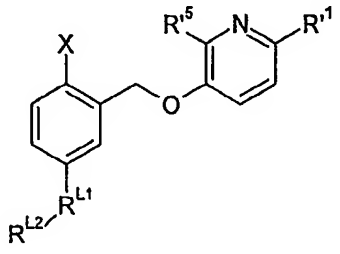
In particular amido, acylamido, ureido, carbamate and reverse carbamate groups are preferred, optionally in combination with a halo group, which is preferably para to the former groups. The former groups are preferably in the 3-position.

If there is one substituent, the ortho and meta positions are preferred, with the meta position being the most preferred. If two substituents are present, it may be preferred that neither is in the para position, unless one is F, when this is preferred to be in the para position.

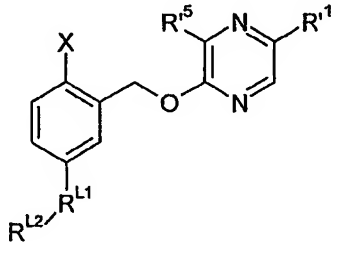
In another embodiment, R^4 is preferably a bicyclic aryl group, where the second ring can be aromatic or non-aromatic (partially or fully saturated). Such groups include napthyl, indole, oxindole, quinoline, isoquinoline, tetrahydroquinoline and tetrahydroisoquinoline.

In a further embodiment, R^4 is preferably a 2,6-dichlorophenyl group. When R^4 is this group, R^5 is preferably H and R^1 is preferably selected from NHR, NHC(=O)R and NHC(=O)NRR', and more preferably NHC(=O)NRR'.

As discussed above, preferred compounds of the present invention are of formulae IIa and IIb:



(IIa)



(IIb)

The preferences for compounds of formula IIa are as follows:

R'1

R'^1 is preferably selected from H and $NR^{C1}R^{C2}$, and more preferably from H and NHR^{C1}. If R'^1 is NHR^{C1}, then R^{C1} is preferably C_{1-4} alkyl (more preferably C_{1-2} alkyl) which may be, and is more preferably, substituted by OH, NH_2, C_{5-20} carboaryl (more preferably C_{5-10} carboaryl, e.g. phenyl), and C_{5-20} heteroaryl (more preferably C_{5-10} heteroaryl, e.g. pyridyl). Examples of preferred R'^1 groups include, but are not limited to, $-NH-C_2H_4-OH$ and $-NH-CH_2-C_6H_5$.

In some embodiments, R'^1 is preferably selected from $NHC(=O)R^{C1}$, $NHC(=O)NR^{C1}R^{C2}$, and $NH_2SO_2R^{C1}$.

R'5

R'^5 is preferably H.

X

X is preferably halo, and more preferably F or Cl, with Cl being most preferred.

R^{L1}

R^{L1} is preferably selected from -NH-C(=O)-, -NH-C(=O)-NH- and -NH-C(=O)-O-, more preferably from -NH-C(=O)- and -NH-C(=O)-NH- and is most preferably -NH-C(=O)-.

In some embodiments, it is preferred that R^{L1} is not -NH-C(=O)-NH-.

R^{L2}

R^{L2} is preferably a C_{5-20} carboaryl or C_{5-20} heteroaryl group, more preferably a C_{5-20} carboaryl group when R^{L1} is -NH-C(=O)- and more preferably a C_{5-20} heteroaryl group when R^{L1} is -NH-C(=O)-NH-.

Particularly preferred are monocyclic carboaryl and heteroaryl groups. If R^{L2} is a carboaryl group, it is preferably phenyl. If R^{L2} is a heteroaryl group it is preferably comprises at least one nitrogen ring atom (e.g. pyrrole, pyridine, thiazole, pyrazole, triazole), and is more preferably pyridine, thiazole or pyrazole, with pyrazole being the most preferred. Heteroaryl groups may be

formed into a moeity by removing a hydrogen from a carbon or hetero ring atom, with the preference being for removal from a carbon ring atom.

The C_{5-20} carboaryl or C_{5-20} heteroaryl group is preferably substituted by one or more substituent groups, more preferably one or two substituents.

When R^{L2} is a six membered ring, it is preferred that at least one substituent group is in the meta position (i.e. β to attachment to R^{L1}), and if there are two substituents these are both preferably in the meta positions.

When R^{L2} is a five membered ring, it is preferred that at least one substituent group is either α or γ to attachment to R^{L1}, with the γ position being preferred.

The substituents are preferably selected from halo (more preferably F and Cl), amino (more preferably cyclic amino groups, and in particular morpholino), C_{1-7} alkyl (more preferably C_{1-4} alkyl, and in particular -Me, -t-Bu and $-CF_3$), C_{5-20} carboaryl groups (more preferably C_{5-10} carboaryl groups, and in particular, phenyl) and C_{5-20} heteroaryl groups (more preferably C_{5-10} heteroaryl groups).

In one aspect of the present invention, preferred compounds of formula **IIa** are those where R^{L1} is -NH-C(=O)- and R^{L2} is a C_6 aryl (carboaryl or heteroaryl) group (more preferably phenyl or pyridyl) bearing a morphplino group, preferably meta to where the C_6 aryl group is joined to R^{L1}, and optionally a halo (more particularly fluoro) group, also preferably meta to where the C_6 aryl group is joined to R^{L1}. In this aspect, R'^5 is preferably H and R'^1 is preferably selected from H and NHR. X is preferably Cl or F, more preferably Cl.

In a further aspect of the present invention, preferred compounds of formula **IIa** are those where R^{L1} is -NH-C(=O)-O- and R^{L2} is a C_6 aryl group (more preferably phenyl). In this aspect R'^5 and R'^1

are preferably H. X is preferably Cl or F, more preferably Cl.

Compounds of the present invention of formula IIa include N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide (44), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (49), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-benzamide (50), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (52), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-isonicotinamide (53), N-[3-(2-Amino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-benzamide (57), N-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (59), 3-Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (60), 1-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-phenyl-urea (61), 3-Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-5-morpholin-4-yl-benzamide (62), [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea (63), 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea (64), 3-tert-Butyl-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (65), N-[3-(Pyridin-3-yloxymethyl)-phenyl]-benzamide (66), 3-Fluoro-5-morpholin-4-yl-N-[3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (67), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-trifluoromethyl-benzamide (69), 3-Chloro-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (70), 1-(5-tert-Butyl-2H-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea (71), 6-Morpholin-4-yl-pyrazine-2-carboxylic acid [4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-amide (75), N-{4-Chloro-3-[6-(2-hydroxy-ethylamino)-pyridin-3-yloxymethyl]-phenyl}-3-fluoro-5-morpholin-4-yl-benzamide (76), N-[3-(6-Benzylamino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (77), 1-(2-tert-Butyl-phenyl)-3-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-urea (78), [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-carbamic acid phenyl ester (79) and 1-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea (81).

Of these compounds, the following are preferred embodiments of compounds of formula IIa: N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide (44), N-[4-Chloro-3-

(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (49), 3-Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-5-morpholin-4-yl-benzamide (62), 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea (64), 3-tert-Butyl-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide (65), N-{4-Chloro-3-[6-(2-hydroxy-ethylamino)-pyridin-3-yloxymethyl]-phenyl}-3-fluoro-5-morpholin-4-yl-benzamide (76), and N-[3-(6-Benzylamino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (77).

The most preferred compounds of the present invention are: N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide (44), N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (49), N-{4-Chloro-3-[6-(2-hydroxy-ethylamino)-pyridin-3-yloxymethyl]-phenyl}-3-fluoro-5-morpholin-4-yl-benzamide (76) and [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-carbamic acid phenyl ester (79).

The preferences for compounds of formula IIb are as follows:

R'1

R'^1 is preferably selected from H and $NR^{C1}R^{C2}$, and more preferably from H and NHR^{C1}. If R'^1 is NHR^{C1}, then R^{C1} is preferably C_{1-4} alkyl (more preferably C_{1-2} alkyl) which may be, and is more preferably, substituted by OH, NH_2, C_{5-20} carboaryl (more preferably C_{5-10} carboaryl, e.g. phenyl), and C_{5-20} heteroaryl (more preferably C_{5-10} heteroaryl, e.g. pyridyl). Examples of preferred R'^1 groups include, but are not limited to, H, $-NH-C_2H_4-OH$ and $-NH-CH_2-C_6H_5$.

In some embodiments, R'^1 is preferably selected from $NHC(=O)R^{C1}$, $NHC(=O)NR^{C1}R^{C2}$, and $NH_2SO_2R^{C1}$.

R'5

R'^5 is preferably H.

X

X is preferably halo, and more preferably F or Cl, with F being most preferred.

RL1

R^{L1} is preferably selected from -NH-C(=O)-, -NH-C(=O)-NH- and -NH-C(=O)-O-, more preferably from -NH-C(=O)- and -NH-C(=O)-NH- and is most preferably -NH-C(=O)-NH-.

In some embodiments, it is preferred that R^{L1} is not -NH-C(=O)-NH-.

RL2

R^{L2} is preferably a C_{5-20} carboaryl or C_{5-20} heteroaryl group, more preferably a C_{5-20} carboaryl group when R^{L1} is -NH-C(=O)-, and more preferably a C_{5-20} heteroaryl group when R^{L1} is -NH-C(=O)-NH-.

Particularly preferred are monocyclic carboaryl and heteroaryl groups. If R^{L2} is a carboaryl group, it is preferably phenyl. If R^{L2} is a heteroaryl group it is preferably comprises at least one nitrogen ring atom (e.g. pyrrole, pyridine, isoxazole, thiazole, pyrazole, thiadiazole, oxadiazole, triazole), and is more preferably pyridine, thiazole, thiadiazole or pyrazole, with

pyrazole being the most preferred. Heteroaryl groups may be formed into a moiety by removing a hydrogen from a carbon or hetero ring atom, with the preference being for removal from a carbon ring atom.

The C_{5-20} carboaryl or C_{5-20} heteroaryl group is preferably substituted by one or more substituent groups, more preferably one or two substituents.

When R^{L2} is a six membered ring, it is preferred that at least one substituent group is in the meta position (i.e. β to attachment to R^{L1}), and if there are two substituents these are both preferably in the meta positions.

When R^{L2} is a five membered ring, it is preferred that at least one substituent group is either α or γ to attachment to R^{L1}, with the γ position being preferred.

When R^{L2} is a nitrogen containing five membered heteroaryl group, it is preferred that one of the nitrogen atoms, and preferably that α to attachment to R^{L1}, is substituted.

The substituents are preferably selected from halo (more preferably F and Cl), amino (more preferably cyclic amino groups, and in particular morpholino), C_{1-7} alkyl (more preferably C_{1-4} alkyl, and in particular -Me, -*i*-Pr, cyclopropyl, -*t*-Bu and $-CF_3$), C_{3-20} heterocyclyl groups (more preferably C_{3-7} heterocyclyl groups, and in particular oxolane and oxane), C_{5-20} carboaryl groups (more preferably C_{5-10} carboaryl groups, and in particular, phenyl), C_{5-20} heteroaryl groups (more preferably C_{5-10} heteroaryl groups, and in particular, pyridine, pyrazine, pyrimidine, thiazole), carboarylalkyl groups (more preferably benzyl) and carboaryloxy groups (more preferably phenyloxy).

The substituents are preferably selected from halo (more preferably F and Cl), amino (more preferably cyclic amino groups, and in particular morpholino), amido (more preferably amido groups where the amino substituents form together with the nitrogen atom to which they are attached a heterocylclic

structure, e.g. N-methyl piperazinyl), sulfonyl (more preferably where the sulfone substituent is a cylic amino group, e.g. morpholino, N-methyl piperazinyl), C_{1-7} alkyl (more preferably C_{1-4} alkyl, and in particular -Me, -*i*-Pr, cyclopropyl, -*t*-Bu and $-CF_3$), C_{3-20} heterocyclyl groups (more preferably C_{3-7} heterocyclyl groups, and in particular oxolane and oxane), C_{5-20} carboaryl groups (more preferably C_{5-10} carboaryl groups, and in particular, phenyl and halo-phenyl, e.g. 4-Cl phenyl, 4-F phenyl and 2,4-diF phenyl), C_{5-20} heteroaryl groups (more preferably C_{5-10} heteroaryl groups, and in particular, pyridine, pyrazine, pyrimidine, thiazole), carboarylalkyl groups (more preferably benzyl) and carboaryloxy groups (more preferably phenyloxy).

In one aspect of the present invention, preferred compounds of formula **IIb** are those where R^{L1} is -NH-C(=O)- and R^{L2} is a C_6 aryl (carboaryl or heteroaryl) group (more preferably phenyl or pyridyl) bearing a morphplino group, preferably meta to where the C_6 aryl group is joined to R^{L1}, and optionally a halo (more particularly fluoro) group, also preferably meta to where the C_6 aryl group is joined to R^{L1}. In this aspect, R'^5 is preferably H and R'^1 is preferably selected from H and NHR. X is preferably Cl or F, more preferably Cl.

In one aspect of the present invention, preferred compounds of formula **IIb** are those where R^{L1} is -NH-C(=O)- and R^{L2} is a C_6 aryl (carboaryl or heteroaryl) group (more preferably phenyl or pyridyl) bearing a morphplino group or N-methyl piperazinyl group, preferably meta to where the C_6 aryl group is joined to R^{L1}, and optionally a halo (more particularly fluoro) group, also preferably meta to where the C_6 aryl group is joined to R^{L1}. In this aspect, R'^5 is preferably H and R'^1 is preferably selected from H and NHR. X is preferably Cl or F, more preferably Cl.

In a further aspect of the present invention, preferred compounds of formula **IIb** are those where R^{L1} is -NH-C(=O)-O- and R^{L2} is a C_6 aryl group (more preferably phenyl). In this aspect R'^5 and R'^1 are preferably H. X is preferably Cl or F, more preferably Cl.

In a further aspect of the present invention, preferred compounds of formula **IIb** are those where R^{L1} is -NH-C(=O)-NH- and R^{L2} is a C_5 heteroaryl group containing at least one nitrogen ring atoms (preferably two), and optionally one sulfur or oxygen ring atom (preferably pyrazole or 1,3,4-thiadiazole), which heteroaryl group is preferably substituted, more preferably with a C_{5-7} aryl or C_{5-7} heterocylic group. The C5-7 aryl substituent group may be, in some embodiments, further substituted by one or more halo groups, such that the group is a, for example, 4-Cl phenyl, 4-F phenyl or 2,4-diF phenyl. These compounds may also be further substituted on the heteroaryl group by a C_{1-7} alkyl group, e.g. t-butyl.

Compounds of the present invention of formula **IIb** include N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (92), N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide (93), N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (94), 1-(5-Cyclopropylmethyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (96), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea (97),
[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester (99), 1-(4-tert-Butyl-thiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (100)
4-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (101), N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-phenoxy-benzamide (102), 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (103), 6-(3H-Benzotriazol-1-yloxy)-2-chloro-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (104), 2-Chloro-6-methoxy-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (105), 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (106), Phenyl-carbamic acid 3-(pyrazin-2-yloxymethyl)-phenyl ester (107), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-[1,3,4]thiadiazol-2-yl)-urea (115), 1-(4,6-Dimethyl-benzothiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (116),

1-[5-(4-Chloro-phenyl)-thiazol-2-yl]-3-[4-fluoro-3-(pyrazin-2-loxymethyl)-phenyl]-urea (117), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-1H-pyrazol-3-yl)-urea (118), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-1H-pyrazol-3-yl)-urea (119), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea (120), 1-(5-Benzyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (121), 3-Methyl-5-phenyl-isoxazole-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (122), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-thiazol-2-yl)-urea (123), 5-(2-Methyl-thiazol-4-yl)-isoxazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (124), 1-[5-tert-Butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (125), 5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (126), 1-[5-tert-Butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (127), 1-[5-(4-Chloro-phenyl)-2-phenyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (128), 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (130), Naphthalene-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (131), 1-[5-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (132), Biphenyl-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (133), 1-(2,5-Diphenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (134), 2-Benzyl-5-tert-butyl-2H-pyrazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (135), 5-tert-Butyl-2-(4-fluoro-benzyl)-2H-pyrazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (136), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea (140), 6-Methyl-imidazo[2,1-b]thiazole-5-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (144), 3,5-Di-tert-butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (146), 1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (147), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-

urea (149), 2,6-Di-morpholin-4-yl-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (150), N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(2-methyl-thiazol-4-yl)-benzamide (151), 1-(2-Benzyl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (153), 1-(2-Benzothiazol-2-yl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (155), 1-[5-tert-Butyl-2-(6-chloro-pyridazin-3-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (156), 1-[5-tert-Butyl-2-(2,6-dimethyl-pyrimidin-4-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (157), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methanesulfinyl-[1,3,4]thiadiazol-2-yl)-urea (159), 1-(5-tert-Butyl-2-pyridin-4-yl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (160), 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-furan-2-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (161), 1-[5-tert-Butyl-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (163), 1-[2-(4-tert-Butyl-phenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (164), 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-pyran-4-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (165), 1-[5-tert-Butyl-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (178), 5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (179), 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazine-1-carbonyl)-benzamide (180), 1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (181), 3-Fluoro-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazin-1-yl)-benzamide, (182) and N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-methyl-piperazine-1-sulfonyl)-benzamide (183).

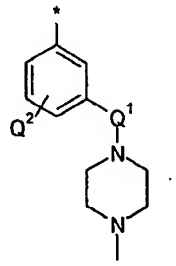
Preferred compounds of formula **IIb** include N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide (93), N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (94), 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (103), 1-(5-tert-Butyl-

2-phenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (106), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-1H-pyrazol-3-yl)-urea (118), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea (120), 1-(5-Benzyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (121), 1-[5-tert-Butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (125), 1-[5-tert-Butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (127), 1-[5-(4-Chloro-phenyl)-2-phenyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (128), 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (130), 1-[5-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (132), 1-(2,5-Diphenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (134), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea (140), 3,5-Di-tert-butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (146), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-urea (149), N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(2-methyl-thiazol-4-yl)-benzamide (151), 1-(2-Benzyl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (153), 1-[5-tert-Butyl-2-(6-chloro-pyridazin-3-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (156), 1-(5-tert-Butyl-2-pyridin-4-yl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (160), 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-furan-2-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (161), 1-[5-tert-Butyl-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (163) 1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-pyran-4-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (165), 1-[5-tert-Butyl-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (178), 5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (179), 3-tert-Butyl-N-[4-fluoro-3-

(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazine-1-carbonyl)-benzamide (180), 1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (181), 3-Fluoro-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazin-1-yl)-benzamide, (182) and N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-methyl-piperazine-1-sulfonyl)-benzamide (183).

Most preferred are N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide (94), 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide (103), 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (106), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-1H-pyrazol-3-yl)-urea (118), 1-[5-tert-Butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (125), 1-[5-tert-Butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (127), 1-[5-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (132), 1-(2,5-Diphenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (134), 1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-urea (149), 1-(5-tert-Butyl-2-pyridin-4-yl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (160) and 1-[5-tert-Butyl-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea (178), 5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (179), 3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazine-1-carbonyl)-benzamide (180), 1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide (181), 3-Fluoro-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazin-1-yl)-benzamide, (182) and N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-methyl-piperazine-1-sulfonyl)-benzamide (183).

One particular preferred class of compounds are those of formula IIb, wherein R'^1 and R'^5 are H, X is halo, preferably F or Cl, R^{L1} is -NH-C(=O), and R^{L2} is of formula III:



(III)

wherein:

Q^1 is selected from a single bond, -C(=O)- and $S(=O)_2$; and

Q^2 is selected from H, halo (preferably H) and C_{1-7} alkyl (preferably t-butyl).

Q^2 is preferably meta to Q^1.

This group of compounds, and their pharmaceutically acceptable salts and/or solvates thereof, are a further aspect of the present invention.

Selective Inhibition

As mentioned above, it is preferred that the compounds of the invention selectively inhibit B-raf kinase over at least one other raf kinase (A-raf and/or C-raf-1). Selectivity of inhibition can be measured by comparing the inhibition of the other raf kinase to that for B-raf kinase. In particular, the figure obtained by dividing the B-raf kinase IC_{50} by the other raf kinase IC_{50}, is a useful measure. It is preferred that this figure is at least 10, more preferably at least 100 and most preferably at least 1000.

Acronyms

For convenience, many chemical moieties are represented using well known abbreviations, including but not limited to, methyl (Me), ethyl (Et), n-propyl (nPr), iso-propyl (iPr), n-butyl (nBu), sec-butyl (sBu), iso-butyl (iBu), tert-butyl (tBu), n-hexyl (nHex), cyclohexyl (cHex), phenyl (Ph), biphenyl (biPh),

benzyl (Bn), naphthyl (naph), methoxy (MeO), ethoxy (EtO), benzoyl (Bz), and acetyl (Ac).

For convenience, many chemical compounds are represented using well known abbreviations, including but not limited to, methanol (MeOH), ethanol (EtOH), iso-propanol (i-PrOH), methyl ethyl ketone (MEK), ether or diethyl ether (Et_2O), acetic acid (AcOH), dichloromethane (methylene chloride, DCM), acetonitrile (ACN), trifluoroacetic acid (TFA), dimethylformamide (DMF), tetrahydrofuran (THF), and dimethylsulfoxide (DMSO).

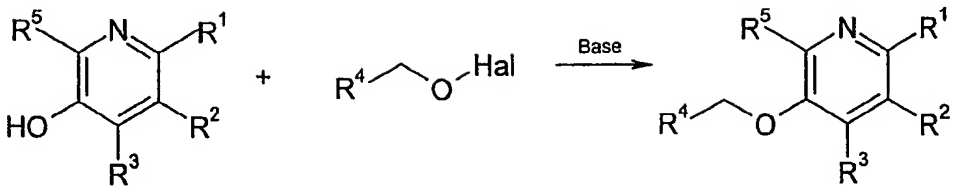
Synthesis Routes

Several methods for the chemical synthesis of compounds of the present invention are described herein. These methods may be modified and/or adapted in known ways in order to facilitate the synthesis of additional compounds within the scope of the present invention. The amounts of reactants given are for guidance. Descriptions of general laboratory methods and procedures, useful for the preparation of the compounds of the present invention, are described in Vogel's Textbook of Practical Organic Chemistry (5^{th} edition, Ed. Furniss, B. S., Hannaford, A.J., Smith, P.W.G., Tatchell, A.R., Longmann, UK). Methods for the synthesis of pyridine containing molecules in particular are described in Heterocyclic Chemistry, Joule, J.A., Mills, R., and Smith, G.F., Chapman & Hall, London.

The synthesis of these compounds is described in the co-pending PCT application filed on 3 July 2002, PCT/GB03/002864, which PCT application is incorporated herein by reference in is entirety.

General routes

The key step in the synthesis of compounds of the present invention is the joining of the pyridine/pyrazine ring to the C_{5-20} aryl group with the intervening $-O-CH_2-$ linkage. As illustrated below, with respect to the pyridine molecule, this is most conveniently achieved by reacting a 3-hydroxy pyridine (or pyrazine) with a halomethyl aryl compound, under basic conditions:

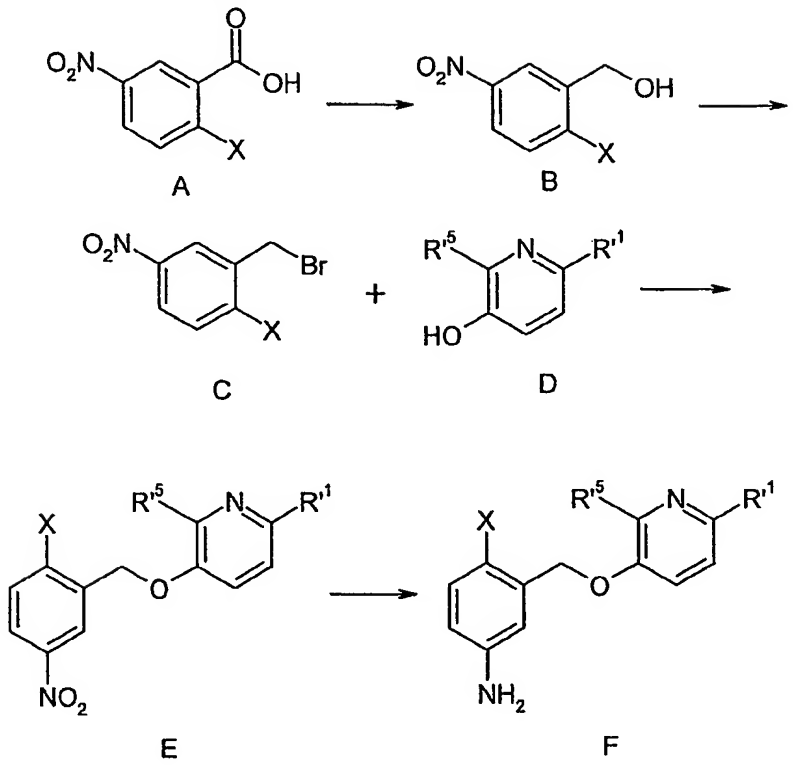


The 3 hydroxy starting material is generally commercially available. The substituents (R^1, R^2, R^3 and R^5) may be in place in the starting material, having been already introduced using known methods, or may be introduced later in the synthesis, as appropriate. Depending on their structure, protection may be needed to carry out the above step.

The halomethyl aryl compounds may be commercially available or readily synthesised using known techniques. One particular technique for deriving these compounds starts from the corresponding aryl carboxylic acid, which is first reduced, for example, using sodium borohydride, followed by halo-de-halogention, achieved, for example, by the use of triphenyl phosphine.

If the aryl group (R^4) bears substituents, then these may either be in place at the beginning of the synthesis, or can be added at any appropriate stage. In particular, certain substituents on the aryl group can be modified, using known reactions.

Synthesis of key intermediates



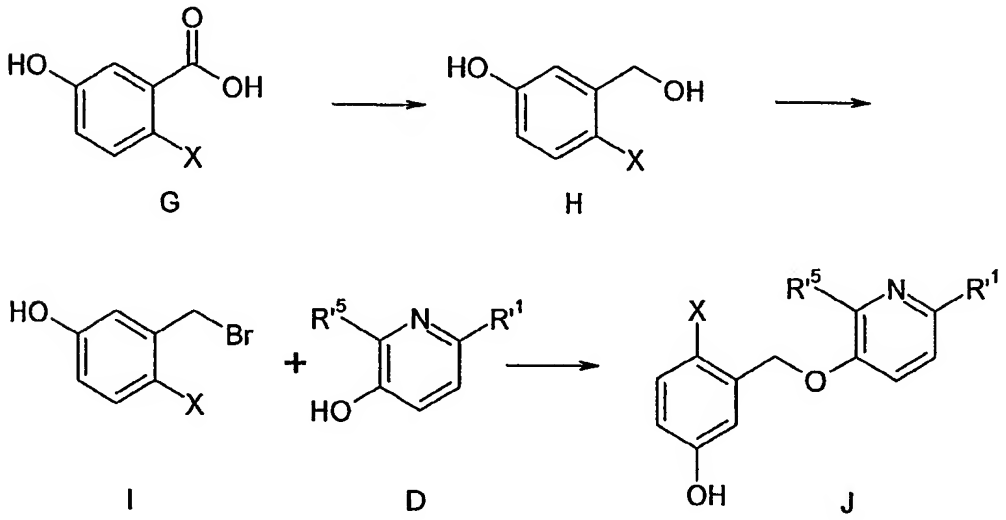
Scheme 1

A key intermediate in the synthesis of preferred compounds of the present invention (i.e. those of formula **IIa**) is the appropriately substituted 3-(pyridin-3-yloxymethyl)-phenylamine (F), as shown in Scheme 1. Scheme 1 illustrates one method of synthesis of this intermediate, although other routes to it are also possible.

The 3-(pyridin-3-yloxymethyl)-phenylamine (F) is synthesised from the corresponding 3-(5-nitro-benzyloxy)pyridine (E) by reduction of the 5-nitro group, using, for example, a metal reducing agent. This 3-(5-nitro-benzyloxy)pyridine (E) is itself synthesised by the base mediated addition of 1-bromomethyl-3-nitro-phenyl (C), or 6-halo equivalent, to the appropriately substituted 3-hydroxy pyridine (D).

The 1-bromomethyl-3-nitro-phenyl (C), or 6-halo equivalent, can be synthesised from the corresponding 3-nitro-benzoic acid (A),

via the (3-nitro-phenyl) methanol (B). The first step is a reduction, using, for example, sodium borohydride, and the second step is a halo-de-hydroxylation, achieved, for example, by the use of triphenyl phosphine and carbon tetrabromide.

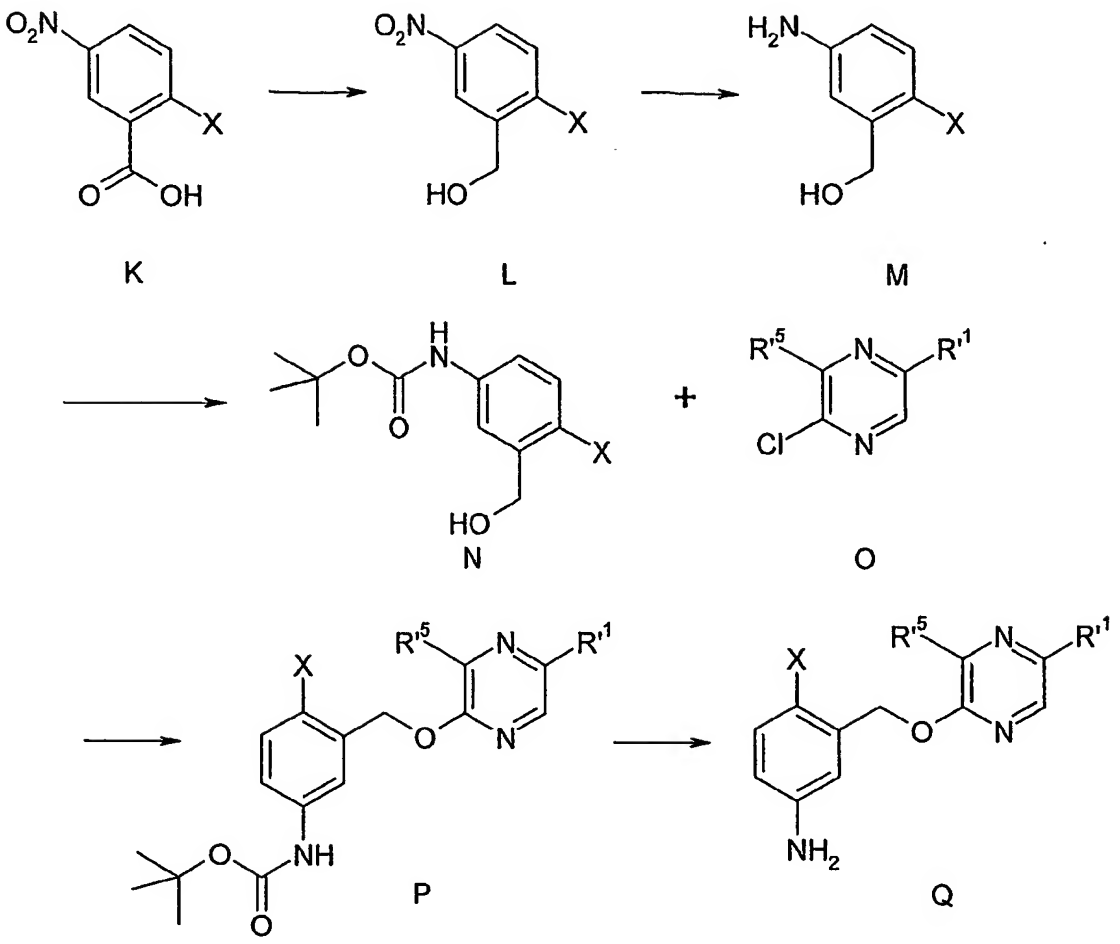


Scheme 2

Another key intermediate in the synthesis of preferred compounds of the present invention (of formula **IIa**) is an appropriately substituted 3-(pyridin-3-yloxymentyl)phenol (J), as shown in Scheme 2. Scheme 2 illustrates one method of synthesis of this intermediate, although other routes to it are possible.

The 3-(pyridin-3-yloxymentyl)phenol (J) is synthesised by the base mediated addition of 1-bromomethyl-3-hydroxy-phenyl (I), or 6-halo equivalent, to the appropriately substituted 3-hydroxy pyridine (D).

The 1-bromomethyl-3-hydroxy-phenyl (I), or 6-halo equivalent, can be synthesised from the corresponding 3-hydroy-benzoic acid (G), via the (3-hydroxy)-phenyl) methanol (H). The first step is a reduction, using, for example sodium borohydride, and the second step is a halo-de-hydroxylation, achieved, for example, by the use of triphenyl phosphine and carbon tetrabromide.

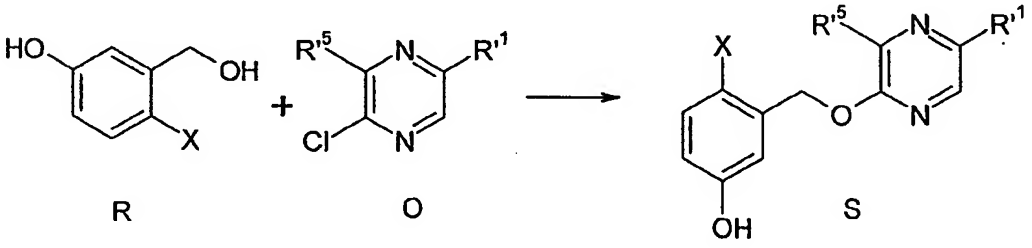


Scheme 3

A key intermediate in the synthesis of further preferred compounds of the present invention (i.e. those of formula **IIb**) is the appropriately substituted 3-(pyrazin-3-yloxymethyl)-phenylamine (Q), as shown in Scheme 3. Scheme 3 illustrates one method of synthesis of this intermediate, although other routes to it are also possible.

The 3-(pyrazin-3-yloxymethyl)-phenylamine (Q) is obtained from the corresponding [3-(pyrazine-3-yloxymethyl)-phenyl] carbamic acid tert-butyl ester (P) by acid mediated deprotection, for example, with a saturate ethyl acetate/HCl solution. The [3-(pyrazine-3-yloxymethyl)-phenyl] carbamic acid tert-butyl ester (P) is synthesised by the base mediated addition of (3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester (N), or its 4-halo eauivalent, to the appropriate 3-chloropyrazine (O).

The (3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester (N) is a protected version of (5-amino-phenyl) methanol (M), or its 2-halo equivalent, the protecting step being carried out using, for example, di-(tert-butylcarbonyloxy)anhydride (BOC anhydride). The (5-amino-phenyl) methanol (M), or its 2-halo equivalent, is itself obtained by reduction of the corresponding (5-nitro-phenyl) methanol (L), for example by hydrogenation using a palladium catalyst. The (5-nitro-phenyl) methanol (L) can be synthesised from the corresponding 5-nitrobenzoic acid (K) by reduction, using, for example, a boron reducing agent.



Scheme 4

Another key intermediate in the synthesis of preferred compounds of the present invention (of formula **IIb**) is an appropriately substituted 3-(pyrazin-3-yloxymentyl)phenol (S), as shown in Scheme 4. Scheme 4 illustrates one method of synthesis of this intermediate, although other routes to it are possible.

The 3-(pyrazin-3-yloxymentyl)phenol (S) is synthesised by the base mediated addition of 3-hydroxy benzyl alcohol (R), or 6-halo equivalent, to the appropriately substituted 3-chloro pyrazine (O).

Detailed routes

R^1

When R^1 is -NRR', one possible method of introducing this substituent is to synthesise the desired compound with R^1=F, and then carry out direct substitution with HNRR'.

When R^1 is -C(=O)NRR', the desired product can be synthesised with R^1 = -C(=O)OH, followed by addition of HNRR', using conventional means to aid amide bond formation (see above).

When R^1 is -NHC(=O)NRR', the desired product can be synthesised with R^1 = -C(=O)OH, which can then be converted to -C(=O)-N_3^-, using, for example thionyl chloride followed by sodium azide, followed by heating to undergo a Curtius rearrangement to the corresponding isocyanate, which then can undergo addition of HNRR' to form the desired final product.

The isocyanate can also be trapped using tert-butanol to yield a tert-butyl protected carbamic acid, which then undergo base mediated substitution of an appropriate halo-compound (Hal-R), to provide an alternative route to compounds where R^1 is NHR.

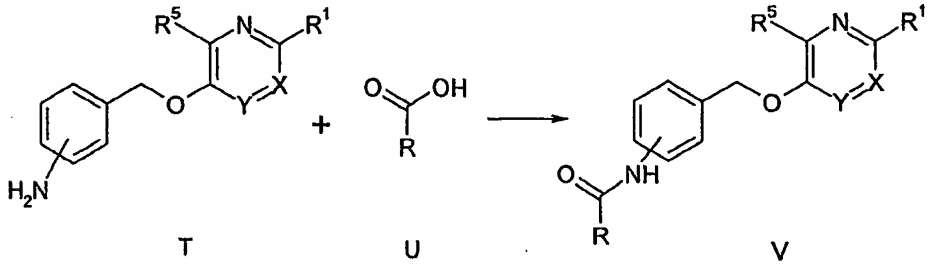
When R^1 is -NHSO$_2$R, the desired product can be synthesised using the methods described in *J. Med. Chem.*, **1991**, 34(4), 1356-1362, JP 57-038777 and *J. Het. Chem.*, **1980**, 17(1), 11-16.

When R^1 is -NH-C(=O)-R, the desired product can be derived from compounds where R^1 = NH_2, by reaction with R-C(=O)OH, or an activated version thereof, for example R-C(=O)Cl.

Derivatising R^4 (illustrated for R^4 = phenyl)

The derivatisation routes shown below in schemes 5 to 8, are particularly applicable to the synthesis of compounds of formulae IIa and IIb from the key intermediates above.

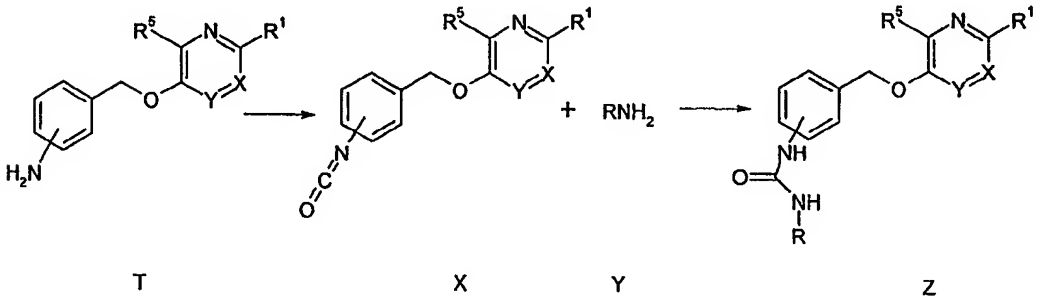
$-NH_2$ to $-NH-C(=O)-R$



Scheme 5

Where it is desired to derivatise $-NH_2$ to $-NH-C(=O)-R$, the desired compound (V) is made by the reaction between the appropriate phenylamine (T) and the aromatic acid (U), or formic acid (where R is H). Due to the relative unreactivity of the phenyl amine, this reaction is usually carried out with the aid of an activator or promoter. Activation of the acid can be achieved by converting it into the corresponding acid chloride, for example, by using oxalyl chloride. An alternative method employs amide bond forming promoters, 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 7-aza-1-hydroxybenzotriazole (HOAt) or 1-hydroxy benzotriazole (HOBt).

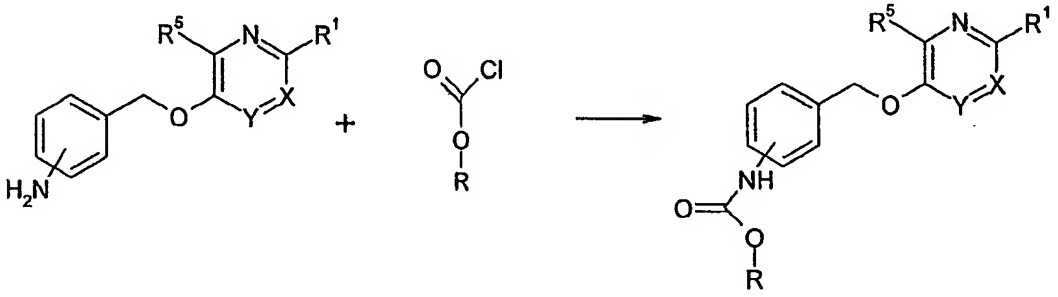
$-NH_2$ to $-NH-C(=O)-NH-R$



Scheme 6

Where it is desired to derivatise $-NH_2$ to $-NH-C(=O)-NH-R$, the desired compound (Z) can be synthesised by the conversion of the appropriate phenylamine (T) to the corresponding isocyanate (X), followed by addition of the appropriate aromatic amine (Y), or ammonium hydroxide (where R=H) without the need for isolation of the isocyanate (X).

$-NH_2$ to $-NH-C(=O)-O-R$

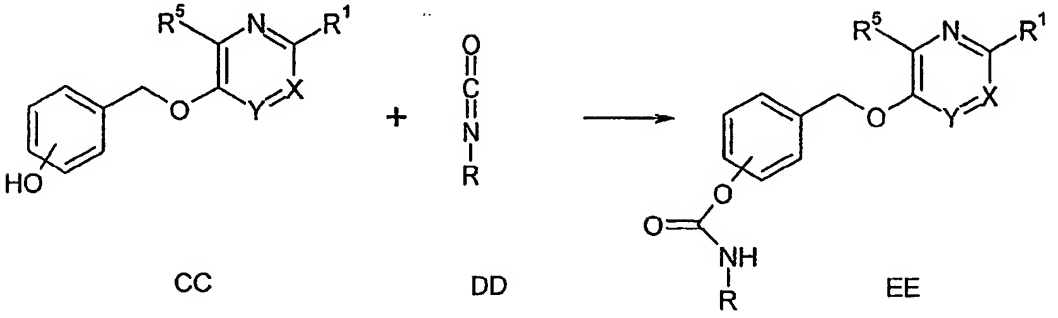


T AA BB

Scheme 7

Where it is desired to derivatise $-NH_2$ to $-NH-C(=O)-O-R$, the desired compound (BB) can be synthesised by the addition of the appropriate aromatic chloroformate (AA) to the appropriate phenylamine (T).

$-OH$ to $-O-C(=O)-NH-R$



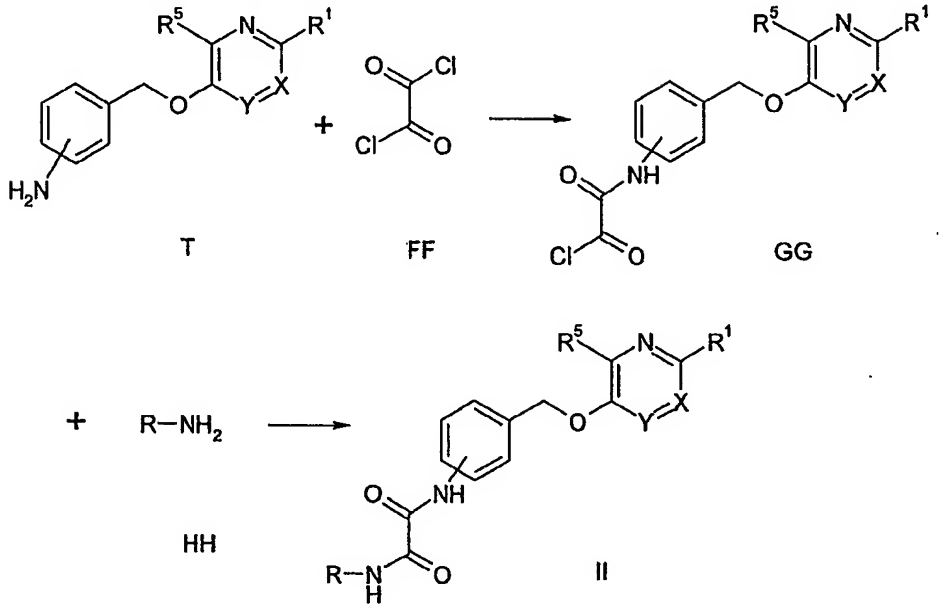
CC DD EE

Scheme 8

The desired compound (EE) is made by the base mediated reaction

between the appropriate phenol (CC) and the aromatic isocynate (DD), or TMS isocyanate (where R is H). An appropriate base would be triethylamine.

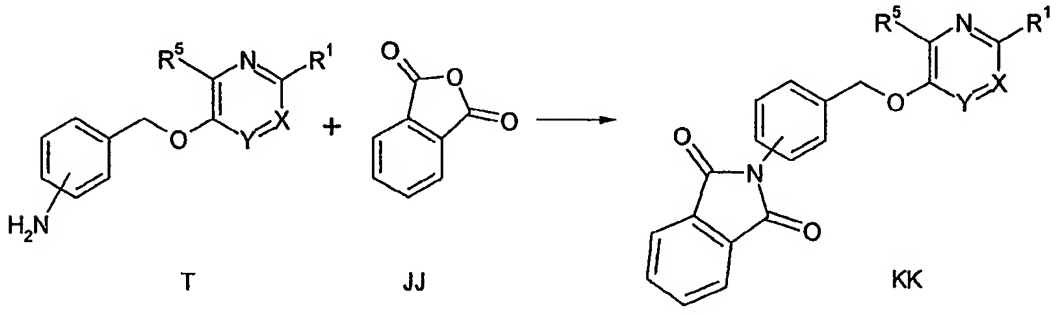
$-NH_2$ to $-NH-C(=O)-C(=O)-NH-R$



Scheme 9

Where it is desired to derivatise $-NH_2$ to $-NH-C(=O)-C(=O)-NH-R$, the desired compound (II) is made via the intermediae GG without isolation. The appropriate phenylamine (T) is first reacted with oxalyl chloride, followed by the appropriate amine (HH) to give the desired oxalamide (II).

$-NH_2$ to -phthalimidyl



Scheme 10

Where it is desired to derivatise $-NH_2$ to -phthalimidyl, the desired compound (KK) is made by reacting phthalic anhydride (JJ) with the appropriate phenylamine (T).

Protection

In the above routes, groups sensitive to the reaction condition can be appropriately protected to avoid side products being formed. For example, in the routes illustrated above, if one of R^1 to R^5 is -OH or -SH, and alkylation with an electrophilic reagent onto HX or Q might be expected to also undesirably substitute these groups, protecting groups for -OH and -SH can be employed (see above discussion of protecting groups).

Use of Compounds of the Invention

The present invention provides active compounds, specifically, active pyrazine derivatives as defined in the first aspect.

The term "active," as used herein, pertains to compounds which are capable of inhibiting raf kinase activity, and specifically includes both compounds with intrinsic activity (drugs) as well as prodrugs of such compounds, which prodrugs may themselves exhibit little or no intrinsic activity.

One of ordinary skill in the art is readily able to determine whether or not a candidate inhibits raf kinase activity and, in particular, B-raf kinase activity. For example, an assay which may conveniently be used in order to assess the inhibition of raf kinase activity offered by a particular compound is described in the examples below.

The invention further provides active compounds for use in a method of treatment of the human or animal body. Such a method may comprise administering to such a subject a therapeutically-effective amount of an active compound, preferably in the form of a pharmaceutical composition.

The term "treatment" as used herein in the context of treating a disease or condition, pertains generally to treatment and

therapy, whether of a human or an animal (e.g. in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the disease or condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the disease or condition, and cure of the disease or condition. Treatment as a prophylactic measure (i.e. prophylaxis) is also included.

The term "therapeutically-effective amount" as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

Active compounds may also be used as part of an *in vitro* assay, for example, in order to determine whether a candidate host is likely to benefit from treatment with the compound in question.

raf inhibitors could be useful in the treatment of diseases in which the raf-MEK-ERK pathway is upregulated by any means.

Screening

Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against raf kinases. For example, a biological sample

taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by elevated expression, activation of a raf kinase (e.g. Braf) or the result of an activating mutation. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of over-expression or activation of raf kinase or a mutation thereof.

The term "marker" include genetic markers including, for example, the measurement of DNA composition to identify mutations of raf, ras, MEK, ERK or a growth factor such as ERB2 or EGFR. The term "marker" also includes markers which are characteristic of up regulation of raf, ras, MEK, ERK, growth factors such as ERB2 or EGFR including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

Methods of identification and analysis of mutations are well known to a person skilled in the art, but typically include methods such as those described in Anticancer Research. 1999 19(4A) 2481-3, Clin Chem. 2002 48, 428 and Cancer Res. 2003 63(14) 3955-7 incorporated herein by reference.

Other tumours which have an up regulated raf-MEK-ERK pathway signal may also be particularly sensitive to inhibitors of raf kinases. A number of assays exist which can identify tumours which exhibit an up regulation in the raf-MEK-ERK pathway, including the commercially available MEK1/2 (MAPK Kinase) assay from Chemicon International. Up regulation can result from over expression or activation of growth factor receptors such as ERB2 and EGFR, or mutant ras or raf proteins.

Typical methods for screening for over expression, up regulation or mutants include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridisation.

In screening by RT-PCR, the level of mRNA for the aforementioned proteins in the tumour is assessed by creating a cDNA copy of the

mRNA followed by amplification of the cDNA by PCR. Methods of PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc., or Innis, M.A. et-al., eds. PCR Protocols: a guide to methods and applications, 1990, Academic Press, San Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook et al. , 2001, 3rd Ed, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference.

An example of an in-situ hybridisation technique would be fluorescence in-situ hybridisation (FISH) (see Angerer, 1987 Meth. Enzymol., 152: 649). Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labeled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. et al., eds. Current Protocols in Molecular Biology, 2004, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in

Molecular Medicine.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour sections, solid phase immunoassay with microtiter plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, and other methods known in the art for detection of specific proteins. Detection methods would include the use of site specific antibodies, such as, phospho raf, phospho ERK or phospho MEK. Inaddition to tumour biopsies other samples which could be utilised include pleural fluid, peritoneal fluid, urine, stool biopsies, sputum, blood (isolation and enrichment of shed tumour cells).

In addition, mutant forms of raf, EGFR or ras can be identified by direct sequencing of, for example, tumour biopsies using PCR and methods to sequence PCR products directly as hereinbefore described. The skilled artisan will recognize that all such well-known techniques for detection of the over expression, activation or mutations of the aforementioned proteins could be applicable in the present case.

Finally, abnormal levels of proteins such as raf, ras and EGFR can be measured using standard enzyme assays, for example for raf those assays described herein.

Cancers

The compounds of the formula (I) are inhibitors of raf kinase activity. As such, they are expected to be useful in providing a means of preventing the growth or inducing apoptosis of neoplasias. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with activating mutants of ras or overexpression of ras may be particularly sensitive to raf inhibitors. Patients with activating mutants of any of the 3 isoforms of raf may also find treatment with raf inhibitors particularly beneficial. Tumours which have other abnormalities leading to an upregulated raf-MEK-ERK pathway signal may also be particularly sensitive to inhibitors of raf kinase. Examples of

such abnormalities include but are not limited to consitutive activation of a growth factor receptor, overexpression of one or more growth factor receptors, overexpression of one or more growth factors, or other mutations or abnormalities leading to upregulation of the pathway.

Examples of cancers which may be treated include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, epidermal, liver, lung, for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, oesophagus, gall bladder, ovary, pancreas e.g. exocrine pancreatic carcinoma, stomach, cervix, thyroid, prostate, or skin, for example squamous cell carcinoma; a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumor of myeloid lineage, for example acute and chronic myelogenous leukemias, myelodysplastic syndrome, or promyelocytic leukemia; thyroid follicular cancer; a tumour of mesenchymal origin, for example fibrosarcoma or habdomyosarcoma; a tumor of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma; xenoderoma pigmentoum; keratoctanthoma; thyroid follicular cancer; or Kaposi's sarcoma.

As mentioned above, it is preferred that the treatment is related to or directed at a mutated form of raf, in particular B-raf, such as the mutations discussed in Wan, P., *et al.*, *Cell*, **116**, 855-867 (2004) and WO 03/056036.

It is also possible that some raf inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine of an inhibitor that inhibits proliferation via the raf-MEK-ERK pathway with another agent which acts via a different mechanism to regulate cell growth or survival or differentiation thus treating several of the characteristic

features of cancer development. Examples of such combinations are set out below.

Such combinations are preferred aspects of the present invention, and accordingly in the aspects of the invention the compounds of formula (I) may be combined with a therapeutic agent as discussed below. Further, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more of the therapeutic agents mentioned below.

Examples of other therapeutic agents that may be administered together (whether concurrently or at different time intervals) with the compounds of the formula (I) include but are not limited to topoisomerase inhibitors, alkylating agents, antimetabolites, DNA binders and microtubule inhibitors (tubulin target agents), such as cisplatin, cyclophosphamide, doxorubicin, irinotecan, fludarabine, 5FU, taxanes, mitomycin C or radiotherapy. For the case of raf kinase inhibitors combined with other therapies the two or more treatments may be given in individually varying dose schedules and via different routes.

In particular, the following agents may be used:

a) topoisomerase I inhibitors, such as camptothecin compounds e.g. topotecan (Hycamtin), irinotecan and CPT11 (Camptosar);

b) antimetabolites, such as anti-tumour nucleosides e.g. 5-Fluorouracil, gemcitabine (Gemzar), raltitrexed (Tomudex), capcitabine (Xeloda), pemetrexed (Alimta), cytarabine or cytosine arabinoside or arabinosylcytosine [AraC] (Cytosar), methotrexate (Matrex), fludarabine (Fludara), tegafur;

c) tubulin targeting agents, such as vinca alkaloids e.g. vincristine (Oncovin), vinorelbine (Navelbine), vinblastine (Velbe); and taxane compounds, e.g. paclitaxel (Taxol), docetaxel (Taxotere);

d) DNA binder and topoisomerase II inhibitors, such as podophyllo-toxin derivatives and anthracycline derivatives e.g. etopside (Eposin, Etophos, Vepeid, VP-16), teniposdie (Vumon), daunorubicin (Cerubidine, DaunoXome), epirubicin (Pharmorubicin), doxorubicin (Adriamycin, Doxil, Rubex), irarubicin (Zavedos),

pegylated liposomal doxorubicin hydrochloride (Caeylx), liposome encapsulated doxorubicin citrate (Myocet), mitoxantrone (Novatrone, Onkotrone);

e) alkylating agents, such as nitrogen mustards or nitrosourea alkylating agents e.g. cyclophosphamide (Endoxana), melphalan (Alkeran), chlorambucil (Leukeran), busulphan (Myleran), carmustine (BiCNU), lomustine (CCNU), ifosfamide (Mitoxana); aziridines, e.g. mitomycin (Mitomycin C Kyoma); platinum compounds, e.g. cisplatin, carboplatin (Paraplatin), oxaliplatin (Eloxatin);

f) monoclonal antibodies, such as EGF family and its receptors and VEGF family and its receptors e.g. trastuzumab (Herceptin), cetuximab (Erbitux), rituximab (Mabthera), tositumomab (Bexxar), gemtuzumab ozogamicin (Mylotarg), Bevacizumab (Avastin);

g) anti-hormones, such as antiandrogens including antiestorgen agents e.g. tamoxifen (Nolvadex D, Soltamox, Tamofen), fulvestrant (Faslodex), raloxifene (Evista), toremifene (Fareston), droloxifene, letrazole (Femara), anastrazole (Arimidex), exemestane (Aromasin), vorozole (Rivizor), bicalutamide (Casodex, Cosudex), luprolide (Zoladex), megestrol acetate (Megace), aminoglutethimide (Cytadren), bexarotene (Targretin);

h) signal transduction inhibitors, e.g. gefitinib (Iressa), imatinib (Gleevec), erlotinib (Tarceva), celecoxob (Celebrex);

i) proteasome inhibitors, e.g. bortezimib (Velcade);

j) DNA methyl transferases, e.g. temozolomide (Temodar); and

k) cytokines and retinoids, e.g. interferon alpha (IntronA, Roferon -A), interleukin 2 (Aldesleukin, Proleukin), All trans-retinoic acid [ATRA] or tretinoin (Vesanoid).

The combination of the agents listed above with a compound of the present invention would be at the discretion of the physician who would select dosages using his common general knowledge and dosing regimens known to a skilled practitioner.

Where the compound of the formula (I) is administered in combination therapy with one, two, three, four or more, preferably one or two, preferably one other therapeutic agents,

the compounds can be administered simultaneously or sequentially. When administered sequentially, they can be administered at closely spaced intervals (for example over a period of 5-10 minutes) or at longer intervals (for example 1, 2, 3, 4 or more hours apart, or even longer periods apart where required), the precise dosage regimen being commensurate with the properties of the therapeutic agent(s).

The compounds of the invention may also be administered in conjunction with non-chemotherapeutic treatments such as radiotherapy, photodynamic therapy, gene therapy; surgery and controlled diets.

For use in combination therapy with another chemotherapeutic agent, the compound of the formula (I) and one, two, three, four or more, preferably one or two, preferably one other therapeutic agents can be, for example, formulated together in a dosage form containing two, three, four or more, preferably one or two, preferably one therapeutic agents. In an alternative, the individual therapeutic agents may be formulated separately and presented together in the form of a kit, optionally with instructions for their use.

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

Particular subsets of cancers include breast cancer, ovarian cancer, colon cancer, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

Particular subsets of cancers may include breast cancer, ovarian cancer, colon cancer, melanoma, prostate cancer, oesophageal cancer, squamous cancer and non-small cell lung carcinomas.

A further subset of cancers may include leukemia, chronic myelogenous leukemia and myelodysplastic syndrome.

Administration

The active compound or pharmaceutical composition comprising the active compound may be administered to a subject by any convenient route of administration, whether systemically/peripherally or at the site of desired action, including but not limited to, oral (e.g. by ingestion); topical (including e.g. transdermal, intranasal, ocular, buccal, and sublingual); pulmonary (e.g. by inhalation or insufflation therapy using, e.g. an aerosol, e.g. through mouth or nose); rectal; vaginal; parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal; by implant of a depot, for example, subcutaneously or intramuscularly.

The subject may be a eukaryote, an animal, a vertebrate animal, a mammal, a rodent (e.g. a guinea pig, a hamster, a rat, a mouse), murine (e.g. a mouse), canine (e.g. a dog), feline (e.g. a cat), equine (e.g. a horse), a primate, simian (e.g. a monkey or ape), a monkey (e.g. marmoset, baboon), an ape (e.g. gorilla, chimpanzee, orang-utan, gibbon), or a human.

The compounds may be administered over a prolonged term to maintain beneficial therapeutic effects or may be administered for a short period only. Alternatively they may be administered in a pulsatile or continuous manner.

Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation) comprising at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

Thus, the present invention further provides pharmaceutical compositions, as defined above, and methods of making a pharmaceutical composition comprising admixing at least one active compound, as defined above, together with one or more pharmaceutically acceptable carriers, excipients, buffers, adjuvants, stabilizers, or other materials, as described herein.

The term "pharmaceutically acceptable" as used herein pertains to compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

Suitable carriers, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations may be in the form of liquids, solutions, suspensions, emulsions, elixirs, syrups, tablets, losenges, granules, powders, capsules, cachets, pills, ampoules, suppositories, pessaries, ointments, gels, pastes, creams, sprays, mists, foams, lotions, oils, boluses, electuaries, or aerosols.

Formulations suitable for oral administration (e.g. by ingestion) may be presented as discrete units such as capsules, cachets or tablets, each containing a predetermined amount of the active compound; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion; as a bolus; as an electuary; or as a paste.

A tablet may be made by conventional means, e.g., compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active compound in a free-flowing form such as a powder or granules, optionally mixed with one or more binders (e.g. povidone, gelatin, acacia, sorbitol, tragacanth, hydroxypropylmethyl cellulose); fillers or diluents (e.g. lactose, microcrystalline cellulose, calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc, silica); disintegrants (e.g. sodium starch glycolate, cross-linked povidone, cross-linked sodium carboxymethyl cellulose); surface-active or dispersing or wetting agents (e.g. sodium lauryl sulfate); and preservatives (e.g. methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sorbic acid). Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active compound therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration (e.g. transdermal, intranasal, ocular, buccal, and sublingual) may be formulated as an ointment, cream, suspension, lotion, powder, solution, past, gel, spray, aerosol, or oil. Alternatively, a formulation may comprise a patch or a dressing such as a bandage or adhesive plaster impregnated with active compounds and optionally one or more excipients or diluents.

Formulations suitable for topical administration in the mouth include losenges comprising the active compound in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active compound in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active compound in a suitable liquid carrier.

Formulations suitable for topical administration to the eye also include eye drops wherein the active compound is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active compound.

Formulations suitable for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of about 20 to about 500 microns which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid for administration as, for example, nasal spray, nasal drops, or by aerosol administration by nebuliser, include aqueous or oily solutions of the active compound.

Formulations suitable for administration by inhalation include those presented as an aerosol spray from a pressurised pack, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichoro-tetrafluoroethane, carbon dioxide, or other suitable gases.

Formulations suitable for topical administration via the skin include ointments, creams, and emulsions. When formulated in an ointment, the active compound may optionally be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active compounds may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least about 30% w/w of a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol and mixtures

thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active compound through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogues.

When formulated as a topical emulsion, the oily phase may optionally comprise merely an emulsifier (otherwise known as an emulgent), or it may comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and/or fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Suitable emulgents and emulsion stabilisers include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate and sodium lauryl sulphate. The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations may be very low. Thus the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required.

Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active compound, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration (e.g. by injection, including cutaneous, subcutaneous, intramuscular, intravenous and intradermal), include aqueous and non-aqueous isotonic, pyrogen-free, sterile injection solutions which may contain anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. Examples of suitable isotonic vehicles for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active compound in the solution is from about 1 ng/ml to about 10 µg/ml, for example from about 10 ng/ml to about 1 µg/ml. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets. Formulations may be in the form of liposomes or other microparticulate systems which are designed to target the active compound to blood components or one or more organs.

Dosage

It will be appreciated that appropriate dosages of the active compounds, and compositions comprising the active compounds, can

vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects of the treatments of the present invention. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, and the age, sex, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, although generally the dosage will be to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration *in vivo* can be effected in one dose, continuously or intermittently (e.g. in divided doses at appropriate intervals) throughout the course of treatment. Methods of determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician.

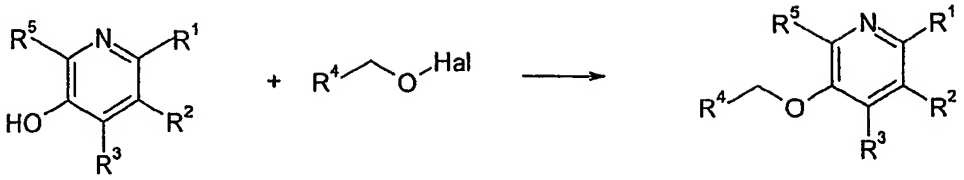
In general, a suitable dose of the active compound is in the range of about 100 pg to about 10 mg, more preferably 10 ng to 1 mg, per kilogram body weight of the subject per day. Where the active compound is a salt, an ester, prodrug, or the like, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

A typical daily dose of the compound can be in the range from 100 picograms to 100 milligrams per kilogram of body weight, more typically 10 nanograms to 10 milligrams per kilogram of bodyweight although higher or lower doses may be administered

where required. Ultimately, the quantity of compound administered will be commensurate with the nature of the disease or physiological condition being treated and will be at the discretion of the physician.

EXAMPLES

Example 1



A mixture of the appropriate starting material (a 3 hydroxy pyridine - generally commercially available) (2.00 mmol), the appropriate halo compound (2.20 mmol) and Adogen™ 464 (1 drop) in aqueous 40% NaOH solution (2 ml) and dichloromethane (2 ml) is stirred at room temperature for 19 hours. The dichloromethane is separated and the aqueous layer diluted with water (10 ml) and then extracted with dichloromethane (3 x 25 ml). The organic extracts are combined, dried (K_2CO_3), filtered and concentrated. Recrystallisation from hexane/dichloromethane or purification using Flash chromatography gives the desired product.

From 2-amino-3-hydroxypyridine

2-amino-3-benzyloxypyridine (**1**) : from benzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.70 (2H, br s), 5.07 (2H, s), 6.59 (1H, dd, J 8, 5), 6.96 (1H, dd, J 8, 1.5), 7.40 (5H, m), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(2-fluorobenzyloxy)pyridine (**3**) : from 2-fluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.66 (2H, br s), 5.13 (2H, s), 6.61 (1H, dd, J 7.5, 5), 7.01 (1H, dd, J 7.5, 1.5), 7.11 (1H, ddd, J 10, 7.5, 1), 7.17 (1H, td, J 7.5, 1), 7.34 (1H, m), 7.44 (1H, tm, J 7.5), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(4-fluorobenzyloxy)pyridine (**4**) : from 4-fluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.67 (2H, br s), 5.02 (2H, s), 6.59 (1H, dd, J 8, 5), 6.95 (1H, dd, J 8, 1.5), 7.08 (2H, t, J 9), 7.39 (2H, dd, J 9, 5), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(1-naphthylmethyloxy)pyridine (**5**) : from 1-naphthylmethyl chloride; δ_H (400 MHz; $CDCl_3$) 4.63 (2H, br s), 5.49 (2H, s), 6.64 (1H, dd, J 8, 5), 7.12 (1H, dd, J 8, 1.5), 7.48 (2H, dd, J 8, 7), 7.55 (2H, m), 7.71 (1H, dd, J 5, 1.5), 7.90

(2H, m), 8.03 (1H, m).

2-amino-3-(2-methoxybenzyloxy)pyridine (**6**) : from 2-methoxybenzyl chloride; δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s), 4.70 (2H, br s), 5.11 (2H, s), 6.59 (1H, dd, J 8, 5), 6.93 (1H, d, J 8), 6.99 (2H, m), 7.32 (1H, m), 7.39 (1H, d, J 7), 7.67 (1H, dd, J 5, 1.5).

2-amino-3-(2-chlorobenzyloxy)pyridine (**8**) : from 2-chlorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.70 (2H, br s), 5.17 (2H, s), 6.59 (1H, dd, J 7.5, 5), 6.96 (1H, dd, J 7.5, 1.5), 7.28 (2H, m), 7.41 (1H, m), 7.47 (1H, m), 7.68 (1H, dd, J 5, 1.5).

2-amino-3-(3-chlorobenzyloxy)pyridine (**9**) : from 3-chlorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.69 (2H, br s), 5.04 (2H, s), 6.59 (1H, dd, J 7.5, 5), 6.93 (1H, dd, J 7.5, 1.5), 7.31 (3H, m), 7.42 (1H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,3-difluorobenzyloxy)pyridine (**12**) : from 2,3-difluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.67 (2H, br s), 5.14 (2H, s), 6.60 (1H, dd, J 7.5, 5), 6.98 (1H, dd, J 7.5, 1.5), 7.10 (1H, m), 7.15 (1H, m), 7.20 (1H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,4-difluorobenzyloxy)pyridine (**13**) : from 2,4-difluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.64 (2H, br s), 5.07 (2H, s), 6.60 (1H, dd, J 8, 5), 6.87 (2H, m), 6.98 (1H, dd, J 8, 1.5), 7.41 (1H, td, J 8.5, 6.5), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(3,4-difluorobenzyloxy)pyridine (**14**) : from 3,4-difluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.66 (2H, br s), 5.00 (2H, s), 6.58 (1H, dd, J 8, 5), 6.91 (1H, dd, J 8, 1.5), 7.18 (3H, m), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2,4-dichlorobenzyloxy)pyridine (**15**) : from 2,4-dichlorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.68 (2H, br s), 5.13 (2H, s), 6.59 (1H, dd, J 8, 5), 6.93 (1H, dd, J 8, 1.5), 7.27 (1H, dd, J 8, 2), 7.40 (1H, d, J 8), 7.43 (1H, d, J 2), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(4-chloro-3-fluorobenzyloxy)pyridine (**16**) : from 4-chloro-3-fluorobenzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.68 (2H, br s), 5.12 (2H, s), 6.60 (1H, dd, J 8, 5), 6.95 (1H, dd, J 8, 1.5), 7.01(1H, J td, 8.5, 2.5), 7.17 (1H, dd, J 8.5, 2.5), 7.44 (1H, dd, J 8.5, 6), 7.69 (1H, dd, J 5, 1.5).

2-amino-3-(2-chloro-4,5-(methylenedioxy)benzyloxy)pyridine (**18**) : from 2-chloro-4,5-(methylenedioxy)benzyl chloride; δ_H (400 MHz; $CDCl_3$) 4.67 (2H, br s), 5.06 (2H, s), 5.98 (2H, s), 6.59 (1H, dd, J 8, 5), 6.87 (1H, s), 6.91(1H, s), 6.94 (1H, dd, J 8, 1.5), 7.68 (1H, dd, J 5, 1.5).

From 3-hydroxypyridine

3-Benzyloxypyridine (**7**) : from benzyl chloride; δ_H (400 MHz; $CDCl_3$) 5.11 (2H, s), 7.21 (1H, ddd, J 8.5, 4.5, 1), 7.25 (1H, ddd, J 8.5, 3, 1.5), 7.39 (5H, m), 8.23 (1H, dd, J 4.5, 1.5), 8.40 (1H, d, J 3).

3-(1-Naphthylmethyloxy)pyridine (**11**) : from 1-naphthylmethyl chloride; δ_H (400 MHz; $CDCl_3$) 5.55 (2H, s), 7.24 (1H, ddd, J 8.5, 4.5, 0.5), 7.34 (1H, ddd, J 8.5, 3, 1.5), 7.54 (4H, m), 7.89 (2H, m), 8.04 (1H, m), 8.26 (1H, dd, J 4.5, 1.5), 8.47 (1H, d, J 3).

From 2-chloro-3-hydroxypyridine

3-Benzyloxy-2-chloropyridine (**10**) : from benzyl chloride; δ_H (400 MHz; $CDCl_3$) 5.19 (2H, s), 7.16 (1H, dd, J 8.0, 4.5), 7.22 (1H, dd, J 8.0, 1.5), 7.32-7.46 (5H, m), 8.00 (1H, dd, J 4.5, 1.5).

The following compounds were made by analogous methods:
2; **17** - MS(ES): m/e 229 (M+H); **19**; **20** - MS(ES): m/e 277 (M+H); **21**; **22**; **23** - MS(ES): m/e 269 (M+H); **25**; **26** - MS(ES): m/e 279 (M+H); **27**; **28**; **29**; **30** - MS(ES): m/e 265 (M+H); **31**; **32** - MS(ES): m/e 255 (M+H); **33**; **34**; **35**; **36**; **37** - MS(ES): m/e 242 (M+H); **38**; **39** - MS(ES): m/e 221 (M+H); **40** - MS(ES): m/e 257 (M+H); **41**; **42** - MS(ES): m/e 250 (M+H); **43** - MS(ES): m/e 277 (M+H); **45** - MS(ES): m/e 245 (M+H); **46** - MS(ES): m/e 521 (M+H); **47** - MS(ES): m/e 241

(M+H); **48** - MS(ES): m/e 314 (M+H); **51** - MS(ES): m/e 360 (M+H); **54** - MS(ES): m/e 340 (M+H); **58**; 73 - MS(ES): m/e 367 (M+H); **74** - MS(ES): m/e 342 (M+H); **80** - MS(ES): m/e 335 (M+H).

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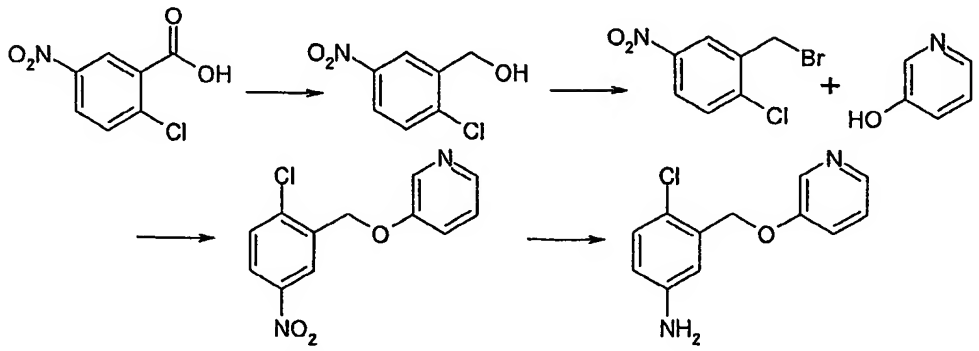
Example 2

(a) Synthesis of key intermediate: 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine



(2-chloro-5-nitro-phenyl)-methanol

To a stirred suspension of sodium borohydride (9.9 mmol) in dry THF (20 ml) at 0°C was added 2-chloro-5-nitrobenzoic acid (4.96 mmol) dissolved in dry THF (5 ml). Boron trifluoride etherate (13.3 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was quenched with 1N HCl and then partitioned between DCM and water. The organic layer was separated, washed with brine solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 0.92g of the desired product; MS(ES): m/e 189 (M+H); δ_H (400 MHz, $CDCl_3$) 8.5 (1H, br s), 8.13 (1H, br dd), 7.54 (1H, d, J 8), 4.89 (2H, s).

2-bromomethyl-1-chloro-4-nitro-benzene

(2-Chloro-5-nitro-phenyl)-methanol (4.9 mmol) was dissolved in DCM (30 ml) and cooled to 0°C. Triphenyl phosphine (5 mmol) was added followed by carbon tetrabromide (4.9 mmol). The reaction mixture was diluted with DCM and washed with water and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to yield 1.23g of the desired product; MS (ES): m/e 252 (M+H); δ_H (400 MHz, $CDCl_3$) 8.37 (1H, br s), 8.15 (1H, dd, J 8, 1), 7.61 (1H, d, J 8), 4.63 (2H, s).

3-(2-chloro-5-nitro-benzyloxy)-pyridine

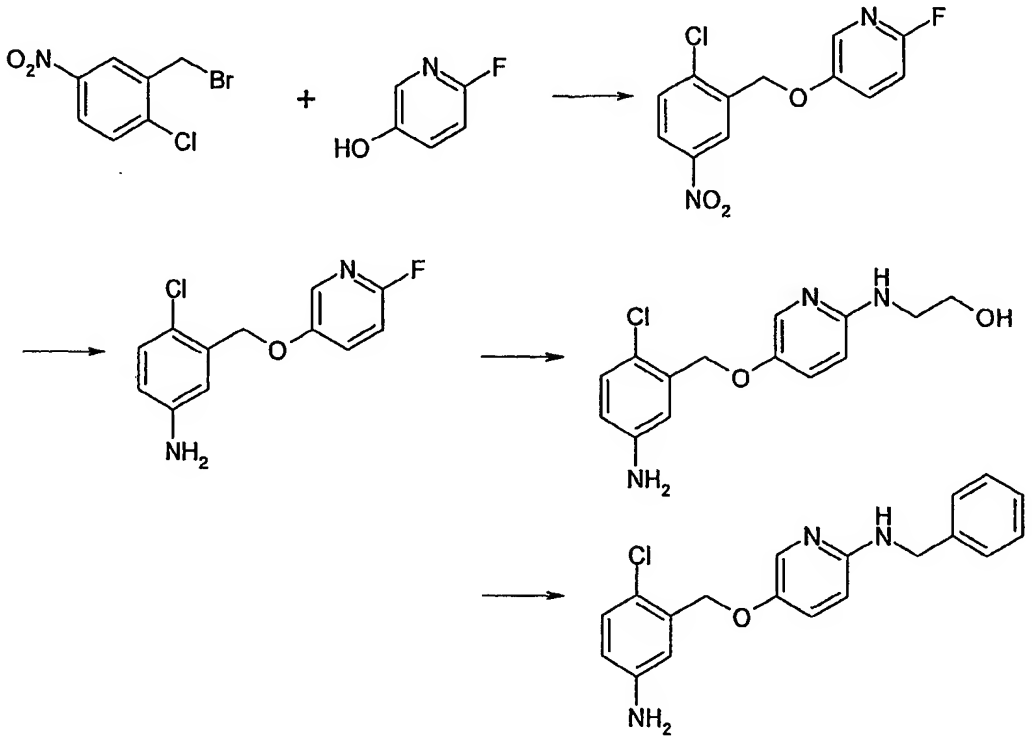
3-Hydroxy pyridine (5.3 mmol) was dissolved in dry DMF (6 ml), cooled to 0°C and then treated with sodium hydride (60%, 5.5 mmol). After 20 mins, 2-bromomethyl-1-chloro-4-nitro-benzene 4.9 mmol) was added in dry DMF (6 ml) and the reaction mixture stirred at 0°C for 1 hour. The reaction mixture was quenched with water, then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 0.32g of the desired product; MS(ES): m/e 266 (M+H).

4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

3-(2-chloro-5-nitro-benzyloxy)-pyridine (1.2 mmol) was dissolved in dioxan:water (5:1, 6 ml), and treated with iron powder (10.9 mmol) and iron sulfate heptahydrate (2.66 mmol). The reaction mixture was refluxed for 6 hours, cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate and washed with saturated bicarbonate and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to give 195mg of the desired product; MS(ES): m/e 236 (M+H).

The corresponding key intermediates 3-(pyridin-3-yloxymethyl)-phenylamine, 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine and 4-chloro-3-(6-hydroxymethylamino-pyridin-3-yloxymethyl)-phenylamine were synthesised in a similar fashion.

(b) Synthesis of key intermediates 4-chloro-3-(6-benzylamino-pyridin-3-yloxymethyl)-phenylamine and 4-chloro-3-(2-amino-pyridin-3-yloxymethyl)-phenylamine



5-(2-Chloro-5-nitro-benzyloxy)-2-fluoro-pyridine

To a solution of 2-fluoro-5-hydroxypyridine (1.77 mmol) in DMF (4 ml) was added NaH (60% dispersion in mineral oil, 4.42 mmol) in small portions at room temperature and under an atmosphere of nitrogen. After stirring for 1 hour, tetra-*n*-butylammonium chloride (17.68 µmol) was added, followed by 2-chloro-5-nitrobenzyl bromide (5.31 mmol)(see above). After stirring for a further 17 hours, MeOH (2 ml) and then water (2 ml) were added. The DMF was removed *in vacuo* and the residue was partitioned between ethyl acetate (50 ml) and water (25 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography eluting with EtOAc/40-60 petroleum ether (1:19) gave the desired compound as a pale yellow oil. δ_H (400 MHz; $CDCl_3$) 5.23 (2H, s), 6.94 (1H, dd, *J* 8.8 and 3.5), 7.46-7.51 (1H, m), 7.61 (1H, d, *J* 8.8), 7.95-7.98 (1H, m), 8.19 (1H, dd, *J* 8.6 and 2.6), 8.49 (1H, d, *J* 2.6).

4-Chloro-3-(6-fluoro-pyridin-3-yloxymethyl)-phenylamine

To a solution of 5-(2-Chloro-5-nitro-benzyloxy)-2-fluoro-pyridine (5.31 mmol) in dioxane/water (5:1, 30 ml) was added iron powder (47.8 mmol) followed by iron sulphate heptahydrate (11.7 mmol) and the reaction mixture was heated to reflux for a period of 17 hours. Upon cooling, the reaction mixture was filtered through a plug of celite, washed with ethyl acetate (250 ml) and the solvent removed *in vacuo*. Purification of the residue by flash chromatography eluting with EtOAc/40-60 petroleum ether (3:7) gave the desired compound. δ_H (400 MHz; d_6-DMSO) 5.07 (2H, s), 5.33 (2H, br s), 6.55 (1H, dd, *J* 8.6 and 2.8), 6.74 (1H, d, *J* 2.8), 7.09 (1H, d, *J* 8.6), 7.14 (1H, dd, *J* 9.1 and 3.0), 7.62-7.68 (1H, m), 7.96 (1H, dd, *J* 3.0 and 1.8).

2-[5-(5-Amino-2-chloro-benzyloxy)-pyridin-2-ylamino]-ethanol

A stirred solution of 4-chloro-3-(6-fluoro-pyridin-3-yloxymethyl)-phenylamine (0.49 mmol) in ethanolamine (2.5 ml) was heated to 130 °C for 24 hours. Upon cooling, the reaction mixture was partitioned between ethyl acetate (80 ml) and water (40 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 ml). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with EtOAc/40-60 petroleum ether (1:1) gave the title compound as a pale yellow oil (85 mg, 56%). δ_H (400 MHz; $CDCl_3$) 3.40-3.44 (2H, m), 3.66 (2H, br s), 3.78 (2H, t, *J* 4.6), 4.66 (1H, br s), 4.99 (2H, s), 6.42 (1H, d, *J* 8.8), 6.55 (1H, dd, *J* 8.6 and 2.8), 6.82 (1H, d, *J* 2.8), 7.12 (1H, d, *J* 8.6), 7.15 (1H, dd, *J* 9.0 and 3.0), 7.80 (1H, d, *J* 2.8).

[5-(5-Amino-2-chloro-benzyloxy)-pyridin-2-yl]-benzylamine

This was prepared in an analogous manner to 2-[5-(5-Amino-2-chloro-benzyloxy)-pyridin-2-ylamino]-ethanol, but using benzylamine in place of ethanolamine. MS(ES): m/e 340 (M+H).

Example 2(a):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-

(a) First method

Synthesis of N-[4-Chloro-3-pyridin-3-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide - **44**

A stirred solution of 2-morpholin-4-yl-isonicotinic acid (0.24 mmol) in dry DCM (5ml) at 0°C was treated with oxalyl chloride (0.29 mmol) and DMF (one drop). The mixture was stirred at 0°C for 1 hour, then the solvent was removed under reduced pressure. The residue was dissolved in dry DCM (3ml) and treated dropwise with 4-chloro-3-(pyridin-2-yloxymethyl)-phenylamine (0.16mmol) and triethylamine (0.16ml) at 0°C. The reaction mixture was allowed to warm to room temperature overnight, then diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 426 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide - **49**, MS(ES): m/e 443 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-fluoro-benzamide - **50**, MS(ES): m/e 358 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **52**, MS(ES): m/e 340 (M+H); N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-isonicotinamide - **53**, MS(ES): m/e 341 (M+H); N-[3-(2-Amino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-benzamide - **57**, MS(ES): m/e 355 (M+H).

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

N-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **59**, MS(ES): m/e 323 (M+H); 3-Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **60**, MS(ES): m/e 341 (M+H); 3-Fluoro-N-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-5-morpholin-

4-yl-benzamide - **62**, MS(ES): m/e 426 (M+H).

from 3-(pyridin-3-yloxymethyl)-phenylamine

N-[3-(Pyridin-3-yloxymethyl)-phenyl]-benzamide - **66**, MS(ES): m/e 305 (M+H).

(b) Second method

*Synthesis of 3-Tert-butyl-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **65***

A stirred solution 4-chloro-3-(pyridin-2-yloxymethyl)-phenylamine (0.14 mmol) in dry DCM (5ml) was treated with EDCI (1.68 mmol) and HOAt (1.68 mmol). 3-Tert-butyl benzoic acid (0.14 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 396 (M+H)

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

From 4-chloro-3-(6-hydroxymethylamino-pyridin-3-yloxymethyl)-phenylamine

N-{4-Chloro-3-[6-(2-hydroxy-ethylamino)-pyridin-3-yloxymethyl]-phenyl}-3-fluoro-5-morpholin-4-yl-benzamide - **76**, MS(ES): m/e 502 (M+H).

from 4-chloro-3-(6-benzylamino-pyridin-3-yloxymethyl)-phenylamine

N-[3-(6-Benzylamino-pyridin-3-yloxymethyl)-4-chloro-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide - **77**, MS(ES): m/e 548 (M+H).

from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-3-trifluoromethyl-benzamide - **69**, MS(ES): m/e 408 (M+H); 3-Chloro-N-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **70**, MS(ES): m/e 374

(M+H).

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

6-Morpholin-4-yl-pyrazine-2-carboxylic acid [4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-amide - **75**, MS(ES): m/e 410 (M+H); 1-(2-tert-Butyl-phenyl)-3-[4-fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - **78**, MS(ES): m/e 394 (M+H).

from 3-(pyridin-3-yloxymethyl)-phenylamine

3-Fluoro-5-morpholin-4-yl-N-[3-(pyridin-3-yloxymethyl)-phenyl]-benzamide - **67**, MS(ES): m/e 408 (M+H).

Example 2(b):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-NH-

Synthesis of 1-(5-tert-Butyl-2H-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - **71**

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) in dry DCM (5 ml) at 0°C was treated with diisopropyl ethylamine (2.13 mmol), followed by triphosgene (0.25 mmol). The mixture was stirred at 0°C for 3 hours, then treated with 3-amino-5-tert-butyl pyrazole (0.42 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated bicarbonate solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 20mg of the desired product; MS(ES): m/e 401 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

from 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine

1-phenyl-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - **61**, MS(ES): m/e 355 (M+H); 1-(5-tert-Butyl-2-phenyl-pyrazol-3-yl)-3-[4-chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea - **64**, MS(ES): m/e 477 (M+H); [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-urea,

63, MS(ES): m/e 279 (M+H), using 2M aqueous ammonium chloride in place of aromatic amine.

from 4-fluoro-3-(pyridin-3-yloxymethyl)-phenylamine

1-[4-Fluoro-3-(pyridin-3-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea - **81**, MS(ES): m/e 388 (M+H).

Example 2(c):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-O-

Synthesis of [4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-carbamic acid phenyl ester - **79**

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) and pyridine in dry DCM (0.5 ml) at 0°C was treated with phenyl chloroformate (0.22 mmol). The reaction mixture was warmed to room temperature over 1 hour then diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 70mg of the desired product; MS(ES): m/e 356 (M+H).

Example 2(d):

Synthesis of further compounds where R^4 is phenyl-N

Synthesis of N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-benzenesulfonamide - 55 and N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-bisbenzenesulfonamide - 56

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.09 mmol) in dry DCM at room temperature was treated with triethylamine (0.18 mmol) and sulfonyl chloride (0.126 mmol). The mixture was stirred at room temperature overnight, then solvent removed under reduced pressure. The residue was diluted with DCM and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of DCM and MeOH afforded the desired products; MS(ES): m/e 376 (M+H) and 516 (M+H).

Synthesis of N-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-N'-(3-fluoro-5-morpholin-4-yl-phenyl)-oxalamide - 72

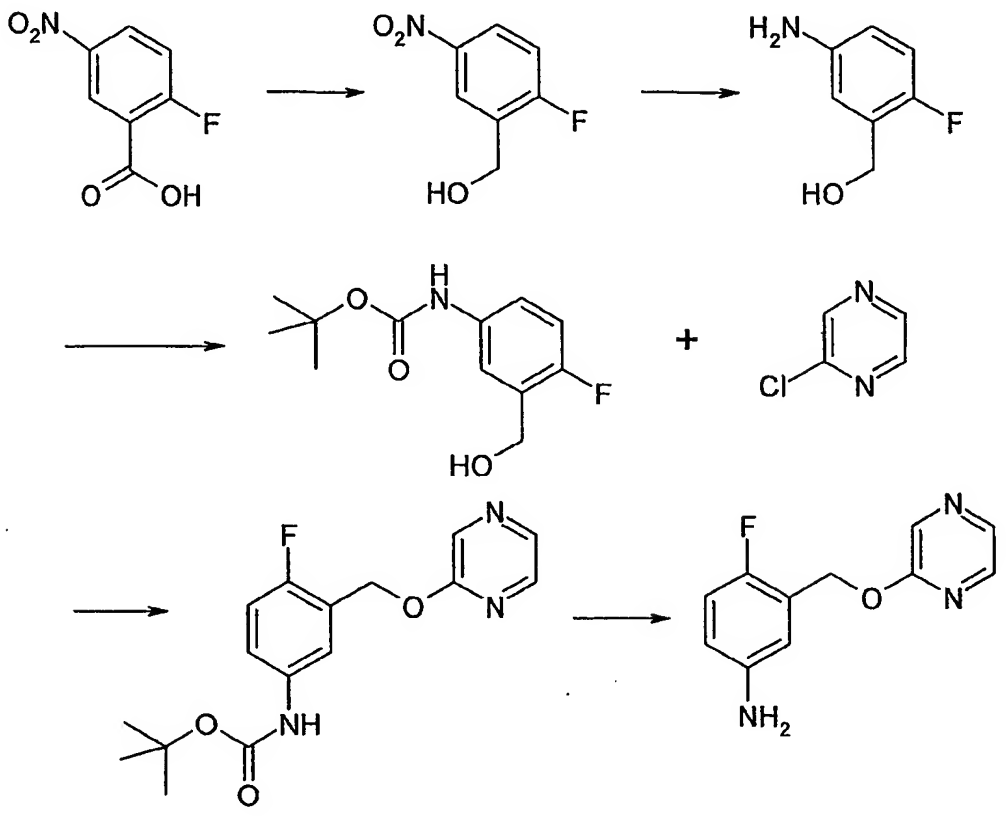
A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.2 mmol) in dry DCM at 0°C was treated with oxalyl chloride (0.2 mmol). The mixture was stirred at room temperature for 1 hour, then treated with aniline (0.4 mmol) and the reaction mixture stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was then diluted with ethyl acetate and washed with 5% citric acid, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by reverse phase HPLC to afford the desired compound; MS(ES): m/e 383 (M+H).

Synthesis of 2-[4-Chloro-3-(pyridin-3-yloxymethyl)-phenyl]-isoindole-1,3-dione - 68

A stirred solution of 4-chloro-3-(pyridin-3-yloxymethyl)-phenylamine (0.21 mmol) in dry chloroform at room temperatute was treated with phthalic anhydride (0.21 mmol). The mixture was stirred at room temperature for 1 hour then solvent removed under reduced pressure. The residue was then redissolved in glacial acetic acid and the reaction mixture refluxed overnight. The reaction mixture was then diluted with ethyl acetate and washed with water, saturated bicarbonate solution and brine solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the title product; MS(ES): m/e 366 (M+H).

Example 3

(a) Synthesis of key intermediate: 4-fluoro-3-(pyrizin-3-yloxymethyl)-phenylamine



(2-fluoro-5-nitro-phenyl)-methanol

To a stirred suspension of sodium borohydride (44.5 mmol) in dry THF (80 ml) at 0°C was added 2-fluoro-5-nitrobenzoic acid (2.43 mmol) dissolved in dry THF (50 ml). Boron trifluoride etherate (66.6 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature over 1 hour. The reaction mixture was quenched with 1N HCl and then partitioned between DCM and water. The organic layer was separated, washed with brine solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 172 (M+H).

(5-Amino-2-fluoro-phenyl)-methanol

(2-fluoro-5-nitro-phenyl)-methanol (0.15 mol) was dissolved in ethanol (100 ml), and treated with 10% Pd/C (15 mmol). The reaction mixture was hydrogenated under an atmosphere of hydrogen gas for 6 hours, then the reaction mixture was filtered through celite. The solvent was evaporated to give the desired compound. MS(ES): m/e 142 (M+H).

(4-Fluoro-3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester

To a stirred solution of (5-Amino-2-fluoro-phenyl)-methanol (12.4 mmol) in dioxan (40 ml) was added di-(tert-butoxycarbonyloxy)anhydride (BOC anhydride) (13.65 mmol) and sodium carbonate (14.89 mmol) in water (40 ml). The reaction mixture was stirred at room temperature overnight, then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 242(M+H).

[4-Fluor-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid tert-butyl ester

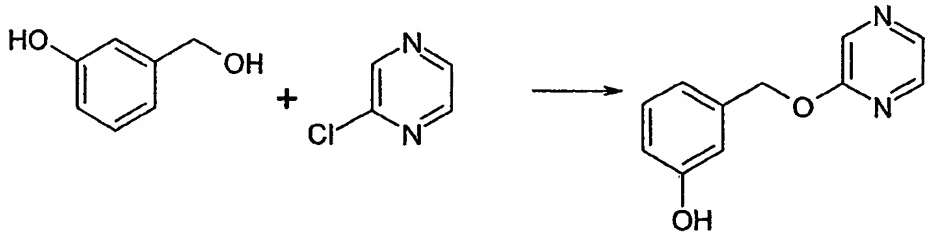
To a stirred solution of (4-Fluoro-3-hydroxymethyl-phenyl)-carbamic acid tert-butyl ester (12.4 mmol) in dry DMF (50 ml) was added sodium hydride (60% dispersion in mineral oil, 25.7 mmol) and the reaction mixture stirred for 30 minutes at room temperature. 2-Chloropyrazine (11.37 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was quenched with water and then partitioned between ethyl and water. The organic layer was separated, washed with brine solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 320 (M+H).

4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine

[4-Fluor-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid tert-butyl ester (9.4 mmol) was treated with saturated ethyl acetate/HCl solution (100ml) at room temperature for 1 hour. The precipitated product was filtered, washed with diethyl ether and dried to afford the desired product. MS(ES): m/e 220 (M+H).

The corresponding key intermediate 4-chloro-3-(pyrazin-2-yloxymethyl)-phenylamine was synthesised in a similar fashion.

(b) Synthesis of key intermediate:3-(pyrazin-2-yloxymethyl)-phenol



3-Hydroxybenzyl alcohol (8.1 mmol) was dissolved in dry DMF (10 ml), treated with sodium hydride (60% suspension in mineral oil, 9 mmol) and stirred at 0°C for 30 minutes. 2-Chloropyrazine (8.1 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1M HCl. The organic layer was separated, washed with saturated sodium bicarbonate solution and brine solution respectively, then dried (MgSO4), filtered and evaporated to afford the desired product. MS(ES): m/e 203 (M+H).

Example 3(a):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-

*Synthesis of N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-phenoxy-benzamide - **102***

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine (0.46 mmol) in dry DMF (4ml) was treated with EDCI (0.55 mmol) and HOBt (0.55 mmol). 3-Phenoxy benzoic acid (0.59 mmol) was added and the reaction mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and

water. The organic layer was washed with saturated bicarbonate solution and brine solution, then the organic layer was separated, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica, eluting with mixtures of petroleum ether and ethyl acetate to afford the desired product. MS(ES): m/e 416 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

from 4-fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine

N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(morpholine-4-sulfonyl)-benzamide - **98**; 4-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **101**, MS(ES): m/e 380 (M+H);

3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **103**, MS(ES): m/e 380 (M+H);

6-(3H-Benzotriazol-1-yloxy)-2-chloro-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **104**, MS(ES): m/e 494 (M+H);

2-Chloro-6-methoxy-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **105**, MS(ES): m/e 391 (M+H);

3-Methyl-5-phenyl-isoxazole-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **122**, MS(ES): m/e 405 (M+H);

5-(2-Methyl-thiazol-4-yl)-isoxazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **124**, MS(ES): m/e 412 (M+H);

5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **126**, MS(ES): m/e 392 (M+H);

Naphthalene-2-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **131**, MS(ES): m/e 374 (M+H);

Biphenyl-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **133**, MS(ES): m/e 400 (M+H);

2-Benzyl-5-tert-butyl-2H-pyrazole-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **135**, MS(ES): m/e 460 (M+H);

5-tert-Butyl-2-(4-fluoro-benzyl)-2H-pyrazole-3-carboxylic acid

[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **136**, MS(ES): m/e 478 (M+H);

6-Methyl-imidazo[2,1-b]thiazole-5-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **144**, MS(ES): m/e 384 (M+H);

3,5-Di-tert-butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **146**, MS(ES): m/e 436 (M+H);

1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **147**, MS(ES): m/e 431 (M+H);

2,6-Di-morpholin-4-yl-pyrimidine-4-carboxylic acid [4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **150**, MS(ES): m/e 496 (M+H);

N-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(2-methyl-thiazol-4-yl)-benzamide - **151**, MS(ES): m/e 421 (M+H) ;

3-tert-Butyl-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazine-1-carbonyl)-benzamide - **180**, MS(ES): m/e 505 (M+H);

3-Fluoro-N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-5-(4-methyl-piperazin-1-yl)-benzamide - **182**, MS(ES): m/e 439 (M+H);

N-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-methyl-piperazine-1-sulfonyl)-benzamide - **183**, MS(ES): m/e 485 (M+H).

from 4-chloro-3-(pyrazin-2-yloxymethyl)-phenylamine

N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-benzamide - **92**, MS(ES): m/e 278 (M+H);

N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-2-morpholin-4-yl-isonicotinamide - **93**, MS(ES): m/e 427 (M+H);

N-[4-Chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-fluoro-5-morpholin-4-yl-benzamide, **94**, MS(ES): m/e 444 (M+H);

5-Phenyl-[1,3,4]oxadiazole-2-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **179**, MS(ES): m/e 407 (M+H);

1-Benzyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid [4-chloro-3-(pyrazin-2-yloxymethyl)-phenyl]-amide - **181**, MS(ES): m/e 446 (M+H).

Example 3(b):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-NH-

Synthesis of 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **106**

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine (0.39 mmol) in dry DCM (10 ml) at 0°C was treated with diisopropyl ethylamine (3.9 mmol), followed by triphosgene (0.46 mmol). The mixture was stirred at 0°C for 3 hours, then treated with 5-tert-butyl-2-phenyl-2H-pyrazol-3-ylamine (0.45 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and saturated bicarbonate solution. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded 20mg of the desired product. MS(ES): m/e 461 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

from 4-fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine

1-(5-Cyclopropylmethyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **96**, MS(ES): m/e 401 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-isopropyl-[1,3,4]thiadiazol-2-yl)-urea - **97**, MS(ES): m/e 389 (M+H);

1-(4-tert-Butyl-thiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **100**, MS(ES): m/e 402 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-[1,3,4]thiadiazol-2-yl)-urea - **115**, MS(ES): m/e 423 (M+H);

1-(4,6-Dimethyl-benzothiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **116**, MS(ES): m/e 424 (M+H);

1-[5-(4-Chloro-phenyl)-thiazol-2-yl]-3-[4-fluoro-3-(pyrazin-2-loxymethyl)-phenyl]-urea - **117**, MS(ES): m/e 457 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-phenyl-1H-pyrazol-3-yl)-urea - **118**, MS(ES): m/e 405 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-1H-pyrazol-3-yl)-urea - **119**, MS(ES): m/e 405 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-

furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea - **120**, MS(ES): m/e 417 (M+H);

1-(5-Benzyl-[1,3,4]thiadiazol-2-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **121**, MS(ES): m/e 437 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(4-phenyl-thiazol-2-yl)-urea - **123**, MS(ES): m/e 422 (M+H);

1-[5-tert-Butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **125**, MS(ES): m/e 497 (M+H);

1-[5-tert-Butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **127**, MS(ES): m/e 496 (M+H);

1-[5-(4-Chloro-phenyl)-2-phenyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **128**, MS(ES): m/e 516 (M+H);

1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **130**, MS(ES): m/e 475 (M+H);

1-[5-(4-Chloro-phenyl)-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **132**, MS(ES): m/e 534 (M+H);

1-(2,5-Diphenyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **134**, MS(ES): m/e 481 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea - **140**, MS(ES): m/e 434 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-urea - **149**, MS(ES): m/e 393 (M+H);

1-(2-Benzyl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **153**, MS(ES): m/e 475 (M+H);

1-(2-Benzothiazol-2-yl-5-tert-butyl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **155**, MS(ES): m/e 519 (M+H);

1-[5-tert-Butyl-2-(6-chloro-pyridazin-3-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **156**, MS(ES): m/e 498 (M+H);

1-[5-tert-Butyl-2-(2,6-dimethyl-pyrimidin-4-yl)-2H-pyrazol-3-yl]-

3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **157**, MS(ES): m/e 491 (M+H);

1-[4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-3-(5-methanesulfinyl-[1,3,4]thiadiazol-2-yl)-urea - **159**, MS(ES): m/e 409 (M+H);

1-(5-tert-Butyl-2-pyridin-4-yl-2H-pyrazol-3-yl)-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **160**, MS(ES): m/e 462 (M+H);

1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-furan-2-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **161**, MS(ES): m/e 493 (M+H);

1-[5-tert-Butyl-2-(4-methanesulfonyl-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **163**, MS(ES): m/e 540 (M+H);

1-[2-(4-tert-Butyl-phenyl)-5-cyclopropyl-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **164**, MS(ES): m/e 501 (M+H);

1-[2-(4-Fluoro-phenyl)-5-(tetrahydro-pyran-4-yl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **165**, MS(ES): m/e 507 (M+H);

1-[5-tert-Butyl-2-(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-[4-fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-urea - **178**, MS(ES): m/e 479 (M+H).

Example 3(c):

Synthesis of compounds where R^4 is phenyl-NH-C(=O)-O-

Synthesis of [4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenyl]-carbamic acid 3-trifluoromethyl-phenyl ester - **99**

A stirred solution of 4-Fluoro-3-(pyrazin-2-yloxymethyl)-phenylamine (0.21 mmol) and pyridine (0.025ml) in DCM (1 ml) at 0°C was treated with 3-trifluoromethyl phenyl chloroformate (0.22 mmol) in DCM (0.2 ml). The mixture was warmed to room temperature over 1 hour, then diluted with DCM, washed with 5% citric acid solution, saturated sodium hydrogen carbonate solution and brine solution. Dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica, eluting with mixtures of petroleum ether and ethyl acetate to afford the desired product. MS(ES): m/e 408 (M+H).

Example 3(d):

Synthesis of compounds where R^4 is phenyl-O-C(=O)-NH-

Synthesis of Phenyl-carbamic acid 3-(pyrazin-2-yloxymethyl)-phenyl ester - **107**

A stirred solution 3-(pyrazin-2-yloxymethyl)-phenol (0.49 mmol) in diethyl ether (10 ml) at room temperature was treated with phenylisocyanate (0.49 mmol) and triethylamine (4 drops). The mixture was stirred at room temperature overnight, then the solid precipitate was filtered off, washed with cold ether and dried. The solid was purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 322 (M+H).

Example 3(e):

Synthesis of compounds where R^4 is dichlorophenyl and R^1 is C(=O)N

*Synthesis of 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-sulfamoyl-ethyl)-amide - **138***

A stirred solution of 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid (0.37 mmol) in dry DMF (5 ml) at room temperature was treated with triethylamine (0.9 mmol), EDCI (0.45 mmol) and HOBt (0.45 mmol). The mixture was stirred at room temperature for 30 mins, then treated with 2-amino-ethanesulfonic acid amide HCl salt (0.45 mmol). The reaction mixture was allowed to warm to room temperature overnight, then solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the desired product. MS(ES): m/e 406 (M+H).

The starting material 5-(2,6-dichloro-benzyloxy)-pyrazine-2-carboxylic acid was prepared as follows:

(i) Lithium-5-chloro-pyrazine-2-carboxylate

5-Chloro-pyrazine-2-carboxylic acid methyl ester (2.9 mmol) was dissolved in tetrahydrofuran/water (5:1, 10ml), treated with

lithium hydroxide (3.04 mmol) and stirred at room temperature overnight. The solvent was removed under reduced pressure to give the desired compound. δ_H (400 MHz, CDCl3) 8.5 (1H, br s), 8.13 (1H, br dd), 7.54 (1H, d, J 8), 4.89 (2H, s).

(ii) 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid 2,6-Dichlorobenzyl alcohol (1.1 mmol) was dissolved in dry DMF (5 ml) and treated with sodium hydride (60% dispersion in mineral oil, 1.21 mmol). The mixture was stirred at room temperature for 30 mins, then treated with lithium-5-chloro-pyrazine-2-carboxylate (1 mmol) and stirred at reflux overnight. The reaction mixture was partitioned between ethyl acetate and water, then the organic layer was separated, dried ($MgSO_4$), filtered, evaporated and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and diethyl ether afforded the title product. MS(ES): m/e 300 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid ethylamide - **111**;

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-ethyl)-amide - **112**;

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide - **113**;

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (2-hydroxy-1-hydroxymethyl-1-methyl-ethyl)-amide - **137**;

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (1,1-dimethyl-2-pyridin-4-yl-ethyl)-amide - **139**.

Example 3(f):

Synthesis of compounds where R^4 is dichlorophenyl and R^1 is NH

Synthesis of 2-[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-ylamino]-ethanol - **158**

A stirred solution of [5-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]carbamic acid tert-butyl ester (0.27 mmol) in dry DMF (5 ml) at room temperature was treated with sodium hydride (60% dispersion in mineral oil, 0.35 mmol). The mixture was stirred at room temperature for 30 mins, treated with (2-bromo-ethoxy)-trimethyl-silane (0.32 mmol) and allowed to reflux overnight. The reaction mixture was partitioned between ethyl acetate and water, the organic layer separated, dried ($MgSO_4$), filtered and evaporated to dryness. The residue was then taken up in dry DCM (5 ml), treated with TFA (0.5 ml) and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica. Elution with mixtures of petroleum ether and ethyl acetate afforded the title product. MS(ES): m/e 315 (M+H).

The starting material [5-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]carbamic acid tert-butyl ester was prepared as follows:

(i) 5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carbonyl azide

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carboxylic acid (14 mmol) was dissolved in thionyl chloride (30 ml) and heated at reflux for 2 hours. The thionyl chloride was removed under reduced pressure with toluene, the residue dissolved in acetone (60 ml), treated with sodium azide (16.9 mmol) and then stirred overnight at room temperature. The reaction mixture was diluted with water and the solvent removed under reduced pressure. The residue was partitioned between DCM and water then the organic layer was separated, dried (MgSO4), filtered and evaporated to afford the title product. MS(ES): m/e 325 (M+H)

(ii) [5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]carbamic acid tert-butyl ester

5-(2,6-Dichloro-benzyloxy)-pyrazine-2-carbonyl azide (0.31 mmol) was dissolved in toluene (2 ml) and treated with t-butanol (0.6 mmol). The mixture was heated to 100°C in a sealed tube for 15 mins, then solvent removed under reduced pressure. The residue

was purified by column chromatography on silica, eluting with mixtures of petroleum ether and ethyl acetate to give the title product. MS(ES): m/e 371 (M+H).

The following compounds were synthesised using a similar method, but with the appropriate starting materials:

Benzyl-[5-(2,6-dichloro-benzyloxy)-pyrazin-2-yl]-amine - **141**;

[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-methyl-amine - **148**;

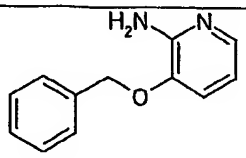
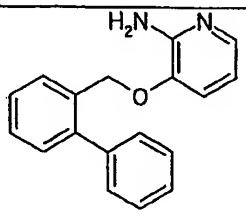
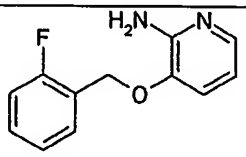
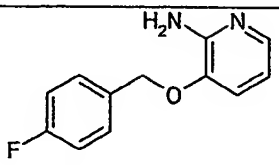
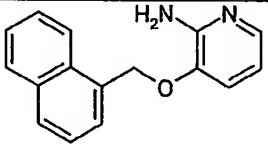
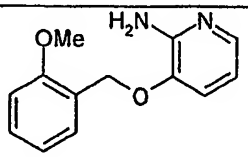
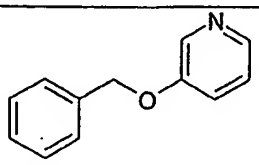
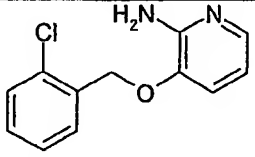
4-[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-morpholine - **152**;

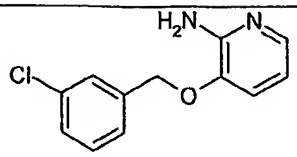
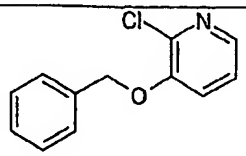
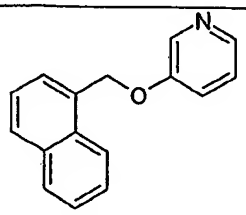
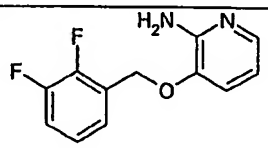
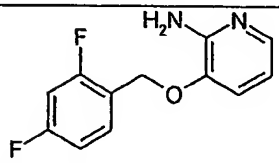
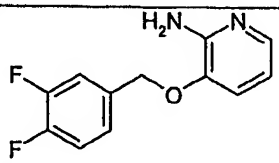
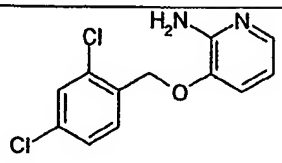
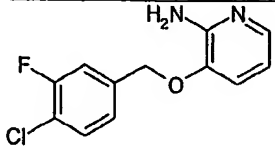
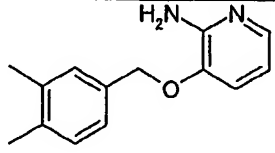
[5-(2,6-Dichloro-benzyloxy)-pyrazin-2-yl]-(1-phenyl-ethyl) -amine - **154**.

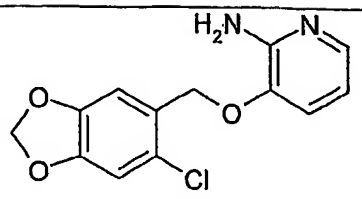
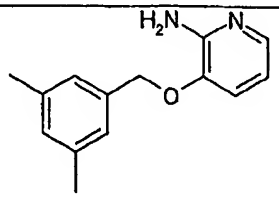
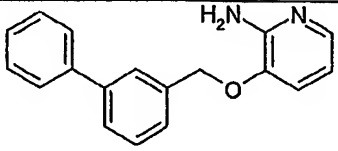
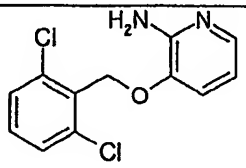
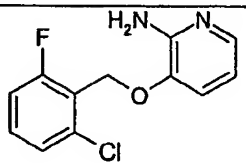
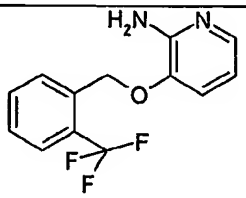
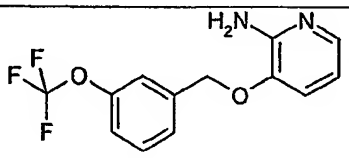
The following compounds were made by analogous methods to those described above:

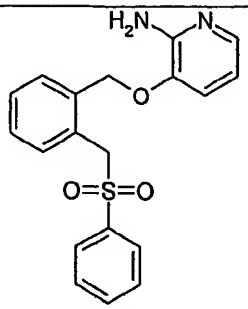
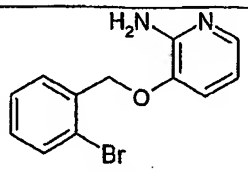
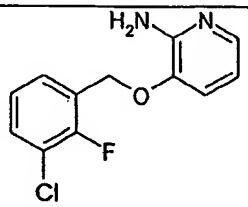
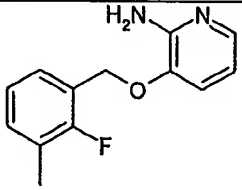
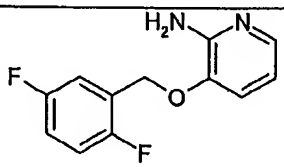
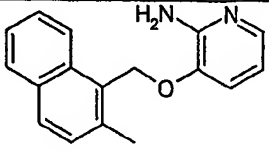
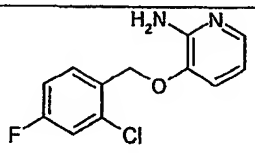
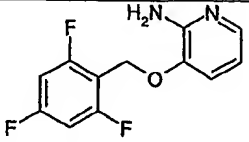
82 - MS(ES): m/e 252 (M+H); **83** - MS(ES): m/e 330 (M+H);**84**; **85** - MS(ES): m/e 236 (M+H); **86** - MS(ES): m/e 202 (M+H); **87** - MS(ES): m/e 255 (M+H); **88**; 89 - MS(ES): m/e 336 (M+H); **90** - MS(ES): m/e 270 (M+H); **91** - MS(ES): m/e 236 (M+H); **95** - MS(ES): m/e 401 (M+H); **108** - MS(ES): m/e 311 (M+H); **109** - MS(ES): m/e 337 (M+H); **110** - MS(ES): m/e 270 (M+H); **114** - MS(ES): m/e 369 (M+H); **129** - MS(ES): m/e 461 (M+H); **142** - MS(ES): m/e 444 (M+H); **143** - MS(ES): m/e 433 (M+H); **145**; **162** - MS(ES): m/e 409 (M+H); **166** - MS(ES): m/e 354 (M+H); **167** - MS(ES): m/e 355 (M+H); **168** - MS(ES): m/e 353 (M+H); **169** - MS(ES): m/e 410 (M+H); **170** - MS(ES): m/e 410 (M+H); **171** - MS(ES): m/e 398 (M+H); **172** - MS(ES): m/e 396 (M+H); **173** - MS(ES): m/e 397 (M+H); **174** - MS(ES): m/e 379 (M+H); **175** - MS(ES): m/e 384 (M+H); **176** - MS(ES): m/e 386 (M+H); **177** - MS(ES): m/e 371 (M+H).

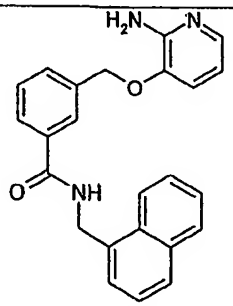
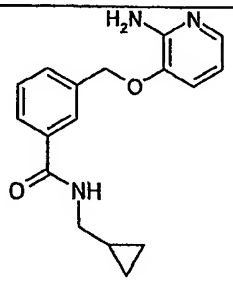
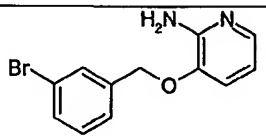
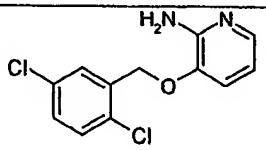
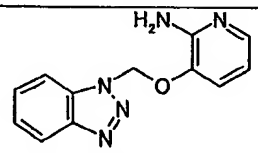
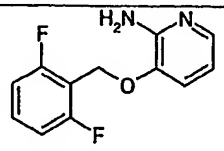
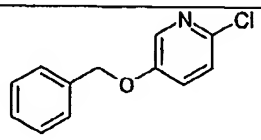
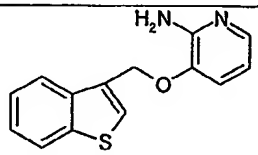
Table 1

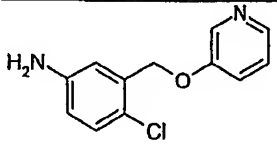
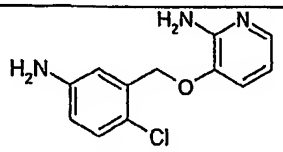
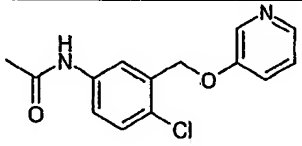
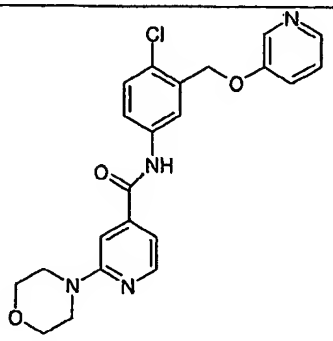
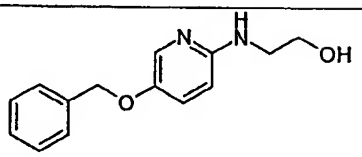
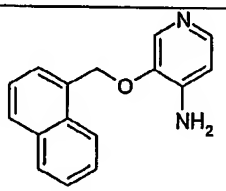
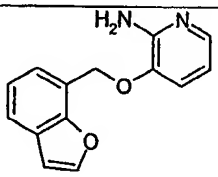
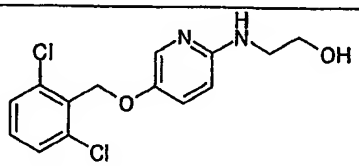
Compound	Structure
1	
2	
3	
4	
5	
6	
7	
8	

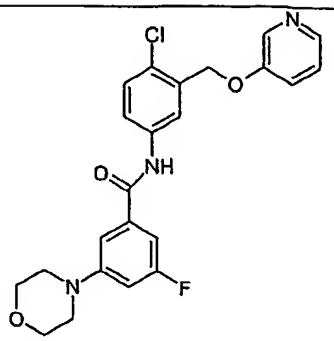
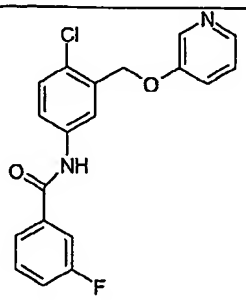
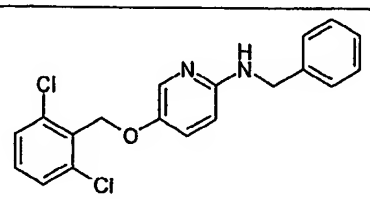
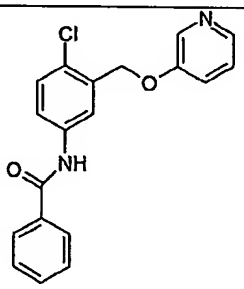
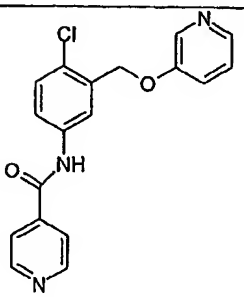
9	
10	
11	
12	
13	
14	
15	
16	
17	

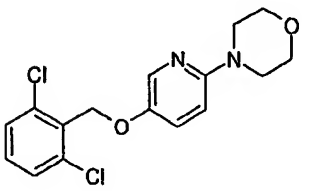
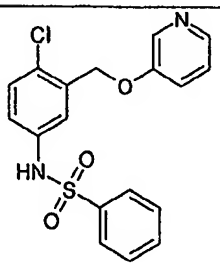
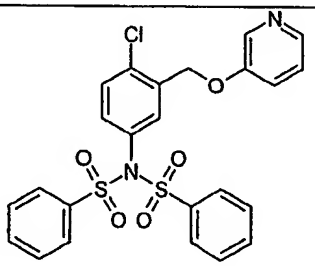
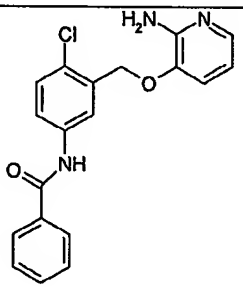
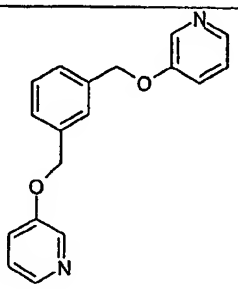
18	
19	
20	
21	
22	
23	
24	

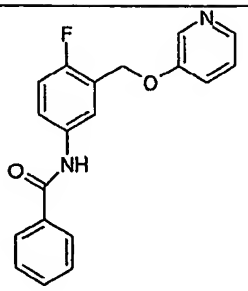
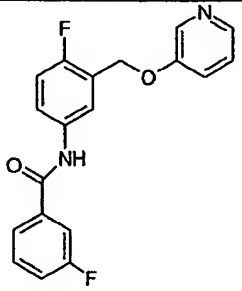
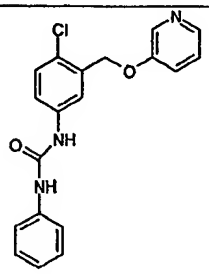
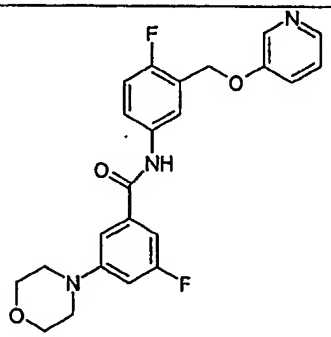
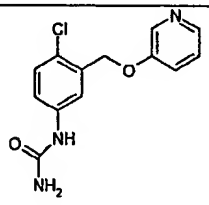
25	
26	
27	
28	
29	
30	
31	
32	

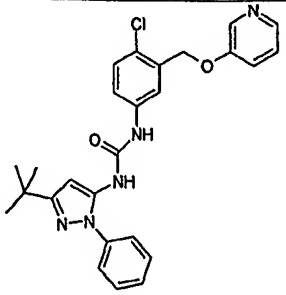
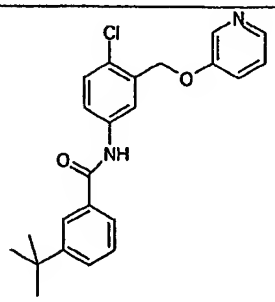
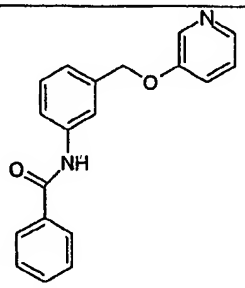
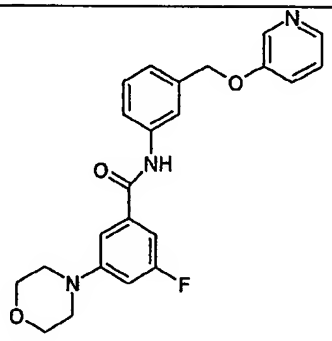
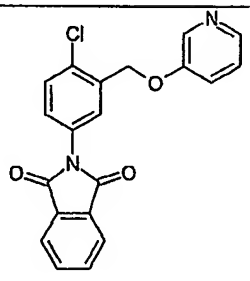
33	
34	
35	
36	
37	
38	
39	
40	

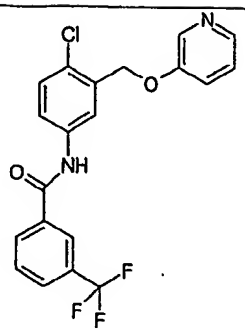
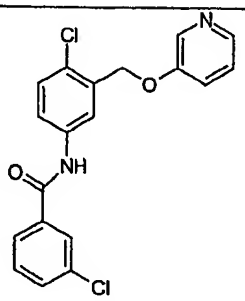
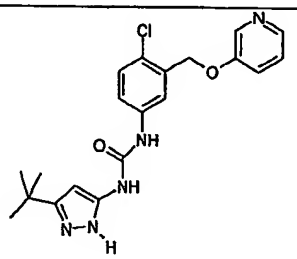
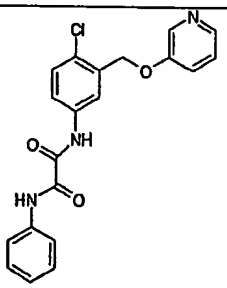
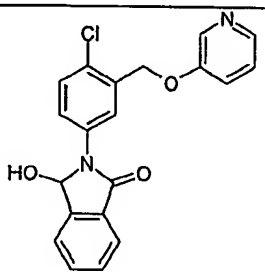
41	
42	
43	
44	
45	
46	
47	
48	

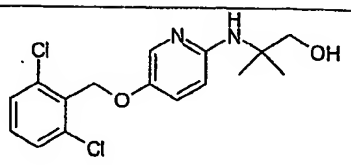
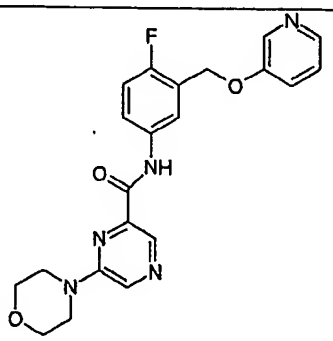
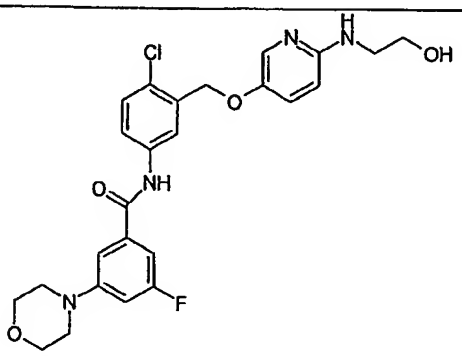
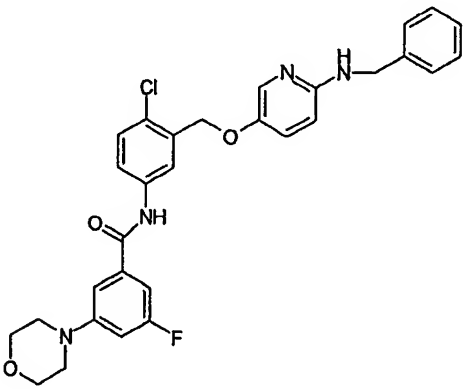
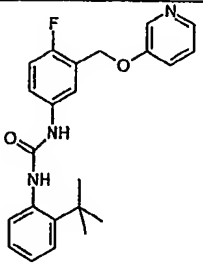
49	
50	
51	
52	
53	

54	
55	
56	
57	
58	

59	
60	
61	
62	
63	

64	
65	
66	
67	
68	

69	
70	
71	
72	
73	

74	
75	
76	
77	
78	

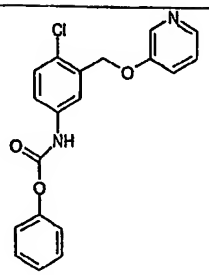
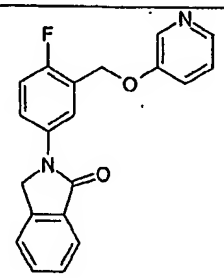
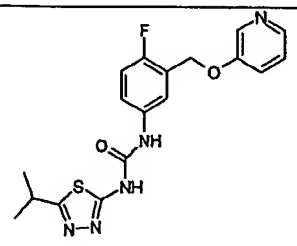
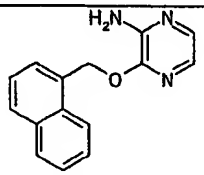
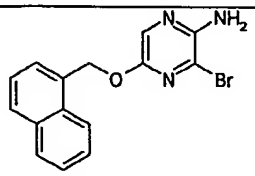
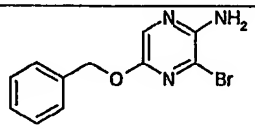
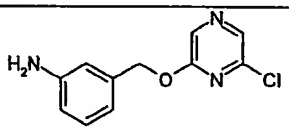
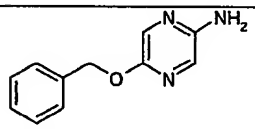
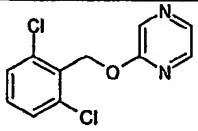
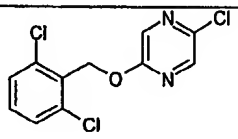
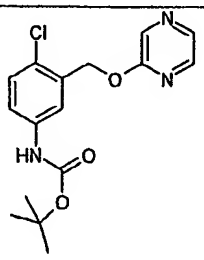
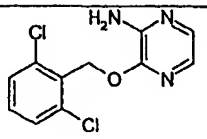
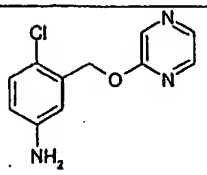
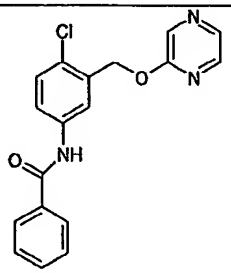
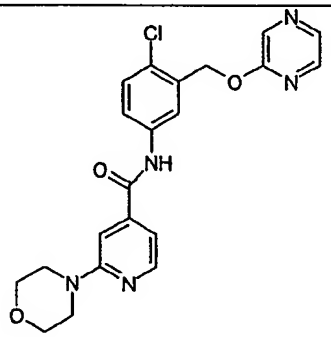
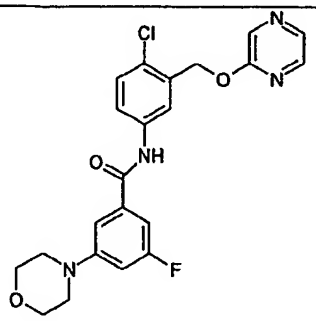
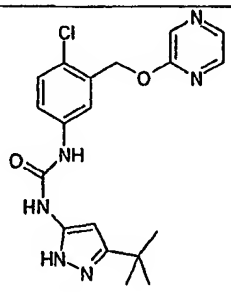
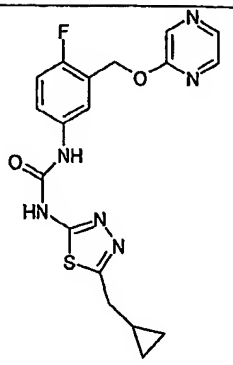
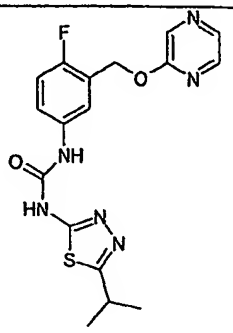
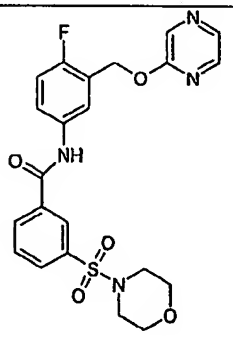
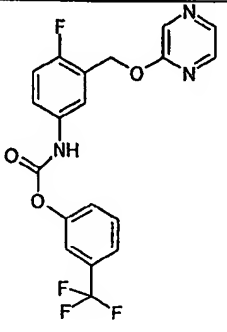
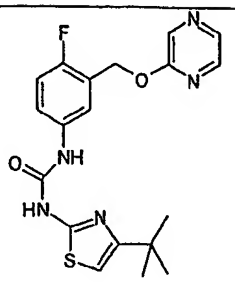
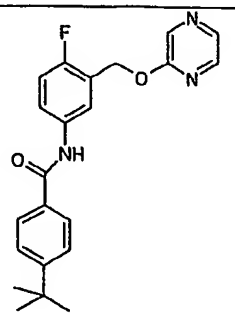
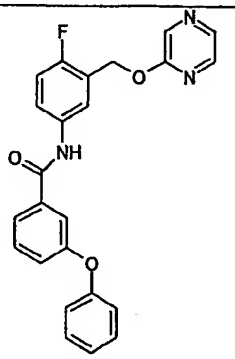
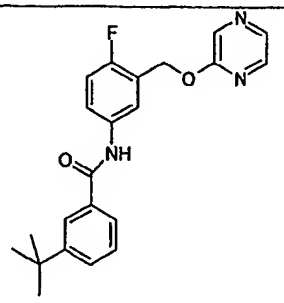
79	
80	
81	

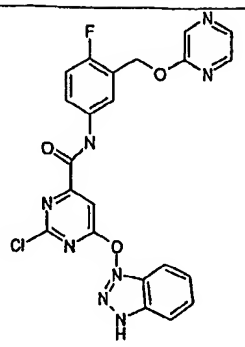
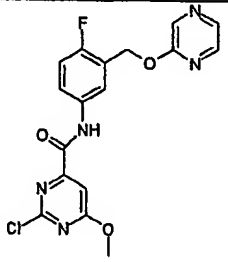
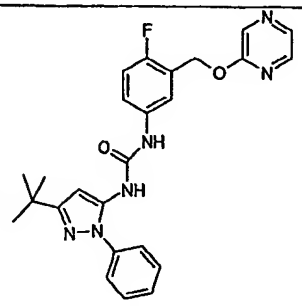
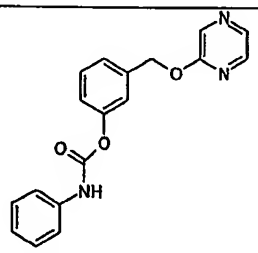
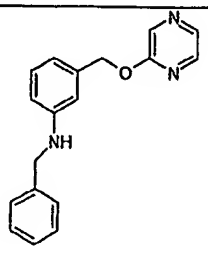
Table 2

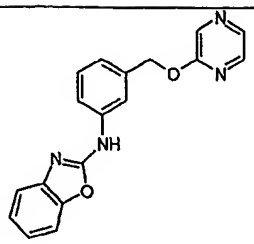
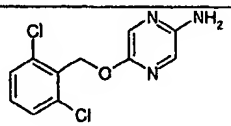
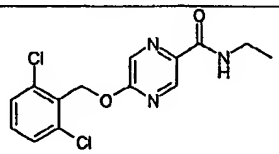
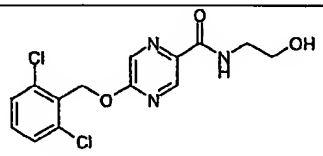
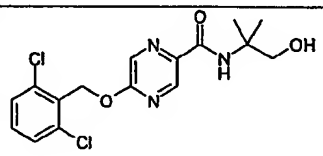
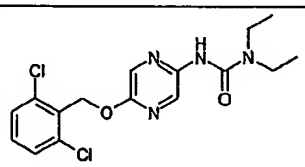
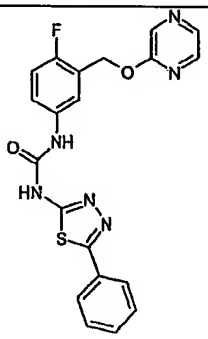
Compound	Structure
82	
83	
84	
85	
86	
87	
88	
89	

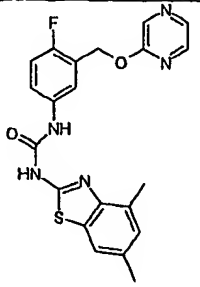
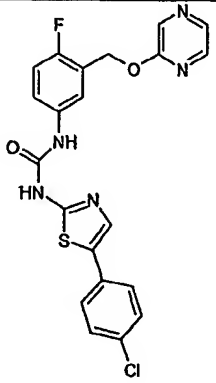
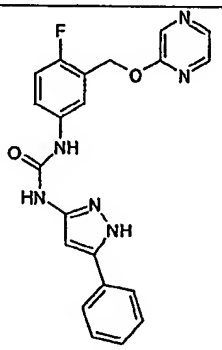
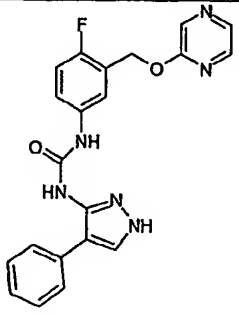
90	
91	
92	
93	
94	
95	

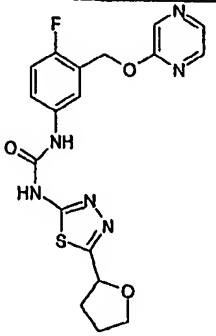
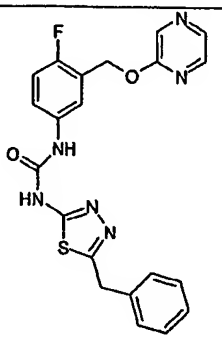
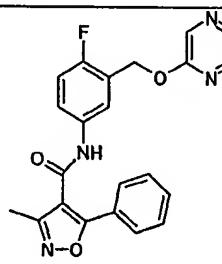
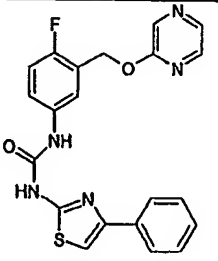
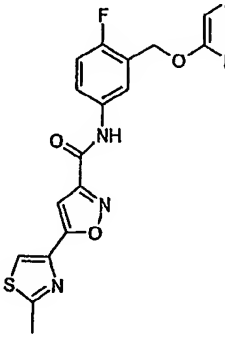
96	
97	
98	
99	

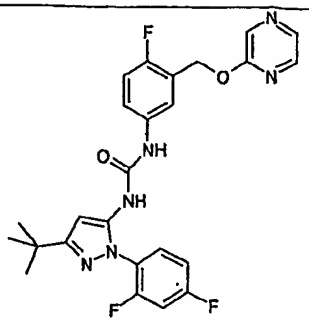
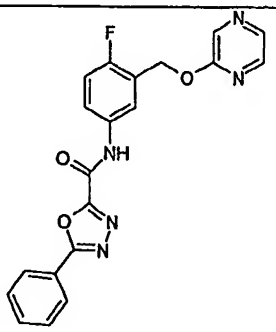
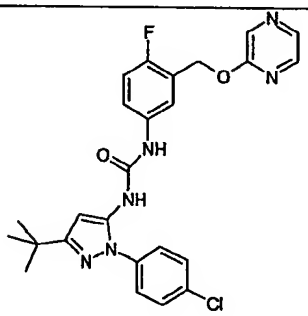
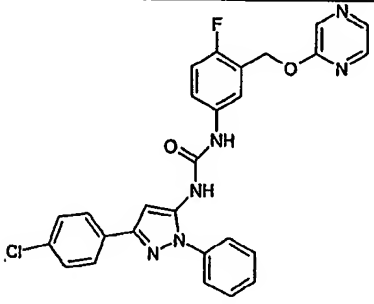
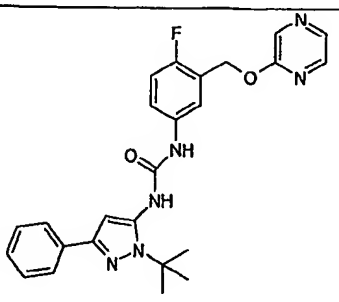
100	
101	
102	
103	

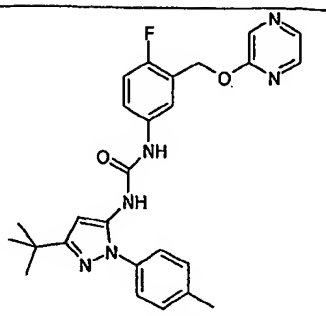
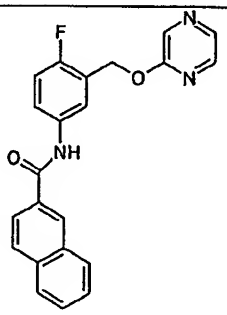
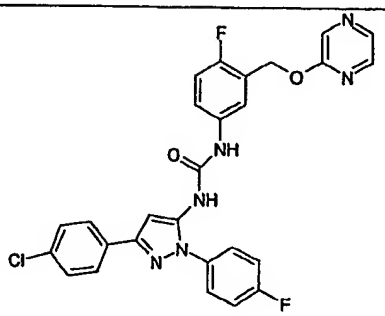
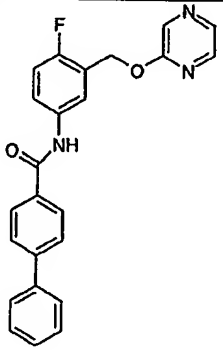
104	
105	
106	
107	
108	

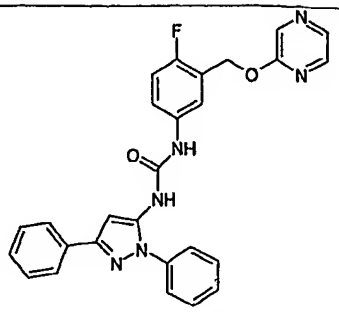
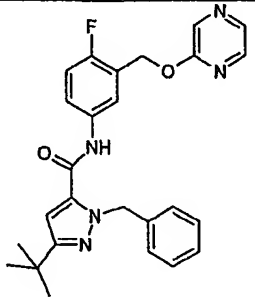
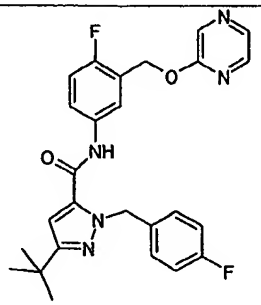
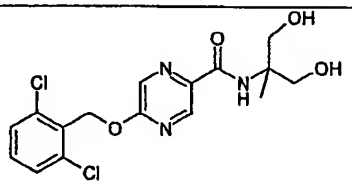
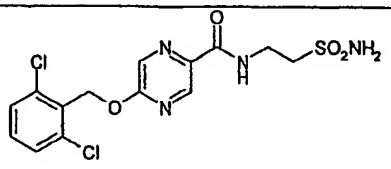
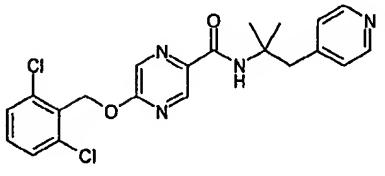
109	
110	
111	
112	
113	
114	
115	

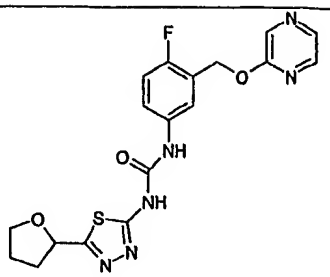
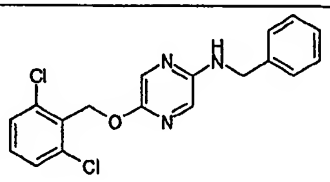
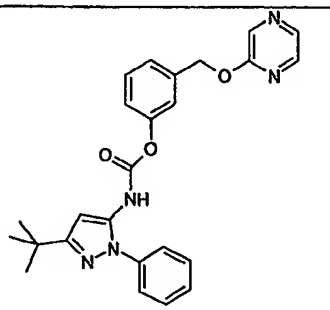
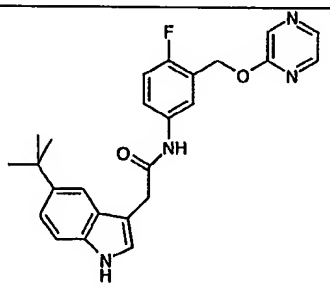
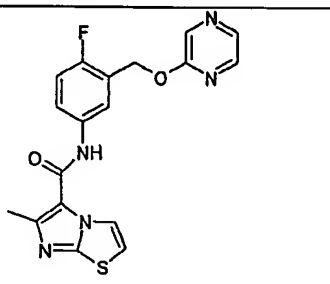
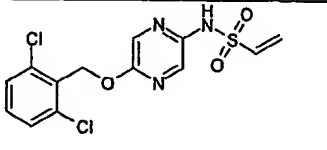
116	
117	
118	
119	

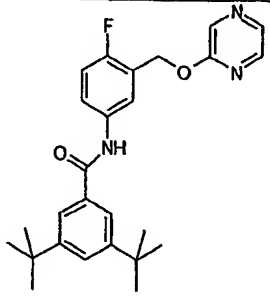
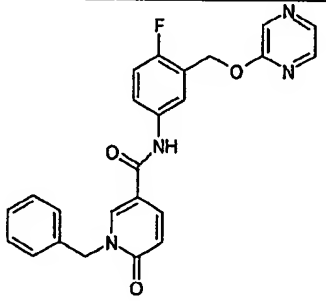
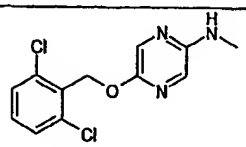
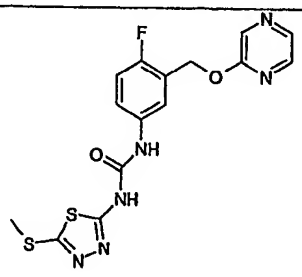
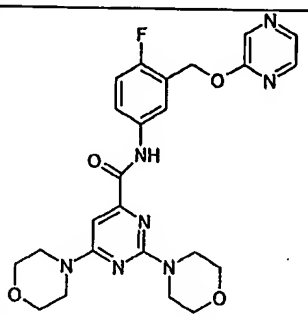
120	
121	
122	
123	
124	

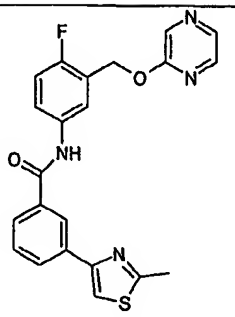
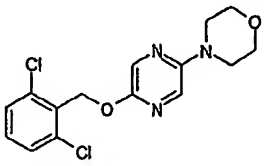
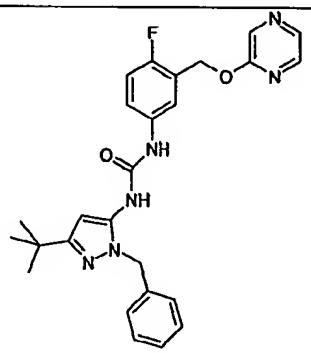
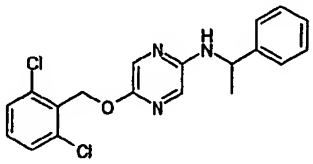
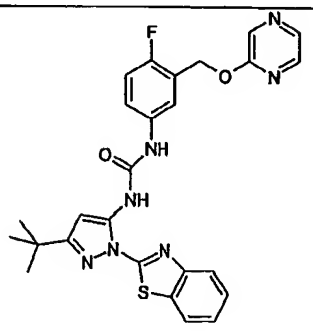
125	
126	
127	
128	
129	

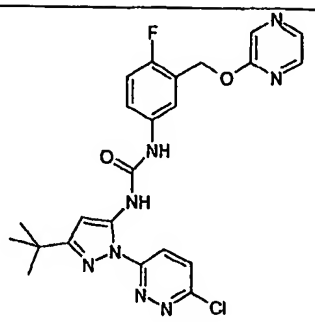
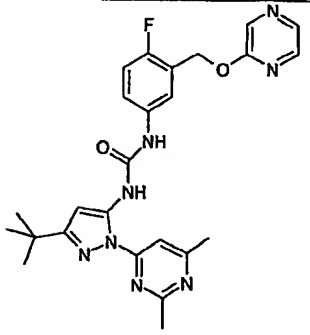
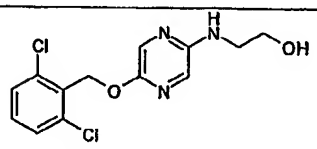
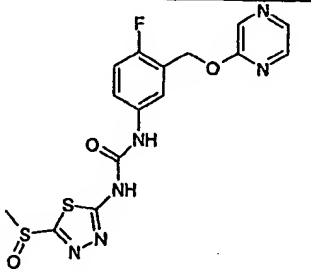
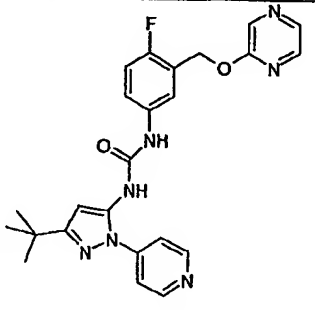
130	
131	
132	
133	

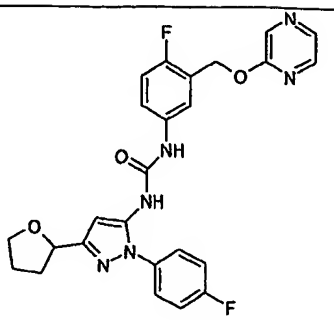
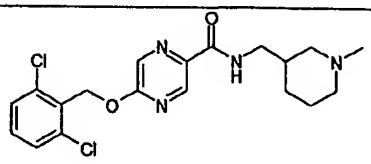
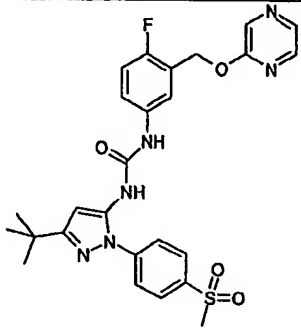
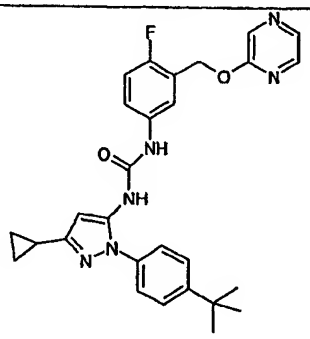
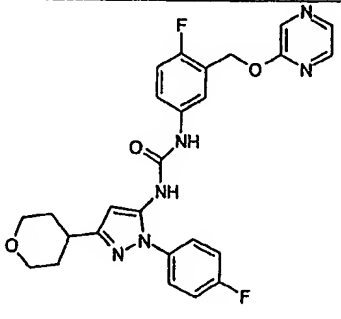
134	
135	
136	
137	
138	
139	

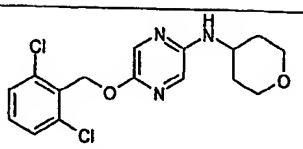
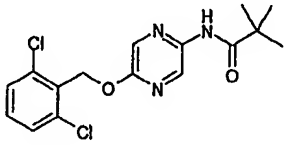
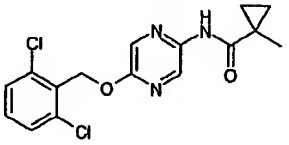
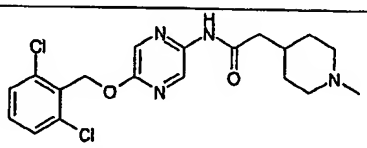
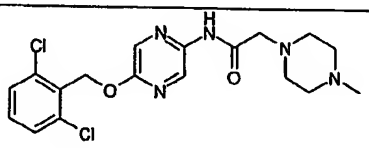
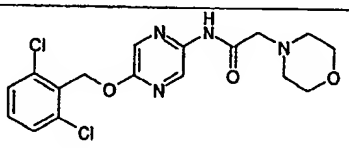
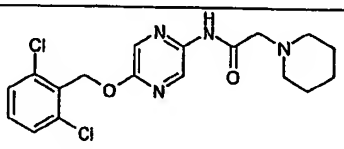
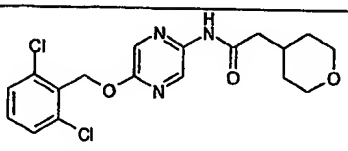
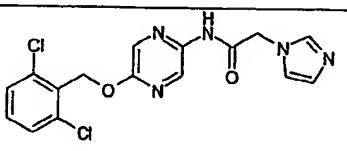
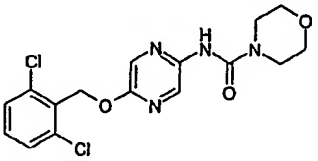
140	
141	
142	
143	
144	
145	

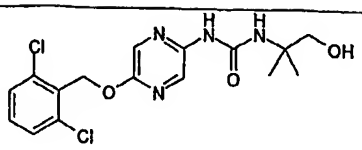
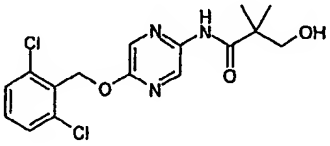
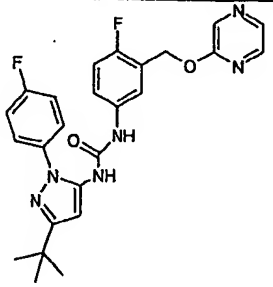
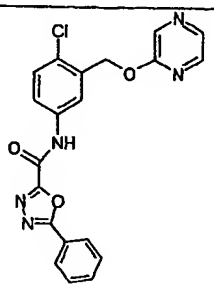
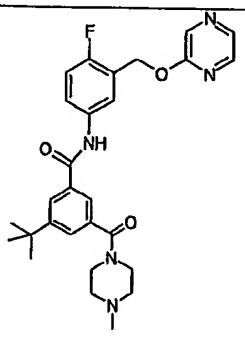
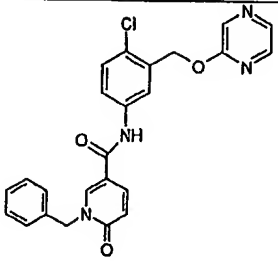
146	
147	
148	
149	
150	

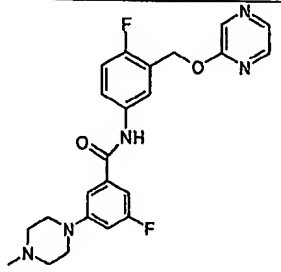
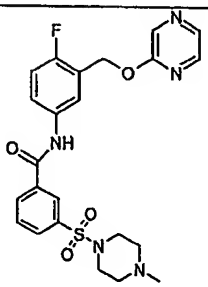
151	
152	
153	
154	
155	

156	
157	
158	
159	
160	

161	
162	
163	
164	
165	

166	
167	
168	
169	
170	
171	
172	
173	
174	
175	

176	
177	
178	
179	
180	
181	

182	
183	

Example 4

(a) B-raf kinase assay

B-raf kinase activity was measured using a 4-tiered cascade enzyme assay similar to that described by Marais R., *et al.*, *J. Biol. Chem.*, **272**, 4378-4383 (1997). B-Raf containing the V599E mutation (Davies, H., *et al.*, *Nature*, **417**, 949 - 954 (2002)) and an N-terminal MDRGSH6 tag was expressed in SF9 insect cells. Detergent soluble extracts from these cells were diluted 1:100 into an assay mixture containing GST-MEK-H6 (6.5µg/ml) and GST-ERK-H6 (100µg/ml) in a buffer containing 800µM ATP and appropriate concentrations of inhibitor or diluent as control. The mixture was incubated for up to 10 minutes at 30°C to activate the ERK in a B-Raf dependent manner within the cascade. The reaction was then stopped by addition of 20mM EDTA. The extent of activation of the GST-ERK was then determined by adding a portion of this quenched reaction mixture to a further reaction containing MBP and 100uM ATP/gamma [^{32}P]ATP. After 12 mins incubation at 30°C the incorporation of [^{32}P] into the MBP substrate, as a measure of B-raf activity, was determined by precipitation with phosphoric acid and isolation by filtration on p81 phosphocellulose paper.

The % inhibition of the B-raf kinase activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the B-raf kinase activity (IC_{50}).

Compounds 94 and 120 have an IC_{50} of less than 0.01 μM and compounds 147 and 165 have an IC_{50} of less than 0.5 μM.

(b) Alternative B-raf assay

B-raf kinase activity was measured using an alternative 4-tiered cascade enzyme assay. B-Raf containing the V599E mutation (Davies, H., *et al.*, *Nature*, **417**, 949 - 954 (2002)) and an N-terminal MDRGSH6 tag was expressed in SF9 insect cells. Detergent soluble extracts from these cells were diluted 1:250 into an assay mixture containing GST-MEK-H6 (25μg/ml), GST-ERK-H6 (281.25μg/ml) and MBP in a buffer containing appropriate concentrations of inhibitor or diluent as control. 0.03 μL (100 μM) ATP was added and the mixture was incubated for up to 10 minutes at 30°C to activate the ERK in a B-Raf dependent manner within the cascade. The extent of activation of the GST-ERK was then determined by adding 0.033 μL (100 μM) HOT $^{32}P\alpha$. After 10 minutes incubation at 30°C the reaction was stopped by isolation of a portion of the reaction mixture on p81 phosphocellulose paper and submersion of this paper in 0.4% orthophosphoric acid. Incorporation of $[^{32}P]$ into the MBP substrate, as a measure of B-raf activity, was determined using a Packard Cernekov counter.

The % inhibition of the B-raf kinase activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the B-raf kinase activity (IC_{50}).

Compounds 117, 128, 129, 132, 134 and 144 have an IC_{50} of less than 100μM. Compounds 93, 95, 98, 102, 115, 151, 157, 181, 182 and 183 have an IC_{50} of less than 10μM. Compounds 99, 100, 101, 106, 125, 126, 127, 140, 153, 160, 161, 162, 178, 179 and 180 have an IC_{50} of less than 1μM.

C-raf kinase Assay

c-raf (human) is diluted to a 10x working stock in 50mM Tris pH

7.5, 0.1mM EGTA, 0.1mM sodium vanadate, 0.1% β-mercaptoethanol, 1mg/ml BSA. One unit equals the incorporation of 1 nmol of phosphate per minute into myelin basic protein per minute.

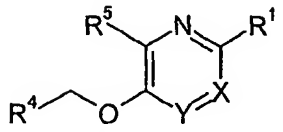
In a final reaction volume of 25µl, c-raf (5-10 mU) is incubated with 25mM Tris pH 7.5, 0.02mM EGTA, 0.66mg/ml myelin basic protein, 10mM MgAcetate, [γ-^{33}P-ATP] (specific activity approx 500cpm/pmol, concentration as required) and appropriate concentrations of inhibitor or diluent as control. The reaction is initiated by the addition of Mg^{2}+[γ-^{33}P-ATP]. After incubation for 40 minutes at room temperature the reaction is stopped by the addition of 5µl of a 3% phosphoric acid solution. 10µl of the reaction is spotted onto a P30 filtermat and washed 3 times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and counting to determine the C-raf activity.

The % inhibition of the C-raf kinase activity is calculated and plotted in order to determine the concentration of test compound required to inhibit 50% of the C-raf kinase activity (IC_{50}).

The following compounds have an IC_{50} of 1µM or less: 44, 49, 76, 79 and 176. The following further compounds have an IC_{50} of 10 µM or less: 167, 168, 170, 171 and 174, whilst the following further compounds have an IC_{50} of 100 µM or less: 169, 172, 173, 175 and 177.

Claims

1. The use of a compound of the formula I:



or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment of a condition ameliorated by the inhibition of raf kinase, wherein:

-X=Y- is selected from $-CR^2=CR^3-$ and $-CR^2=N-$;

R^1 is selected from H, halo, NRR', NHC(=O)R, NHC(=O)NRR', NH_2SO_2R, and C(=O)NRR', where R and R' are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, SO_2-NH_2, C_{5-20} carboaryl, C_{5-20} heteroaryl and C_{3-20} heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group;

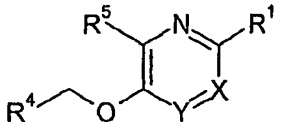
R^2 and R^3 (where present) are independently selected from H, optionally substituted C_{1-7} alkyl, optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino;

R^4 an optionally substituted C_{5-20} carboaryl or C_{5-20} heteroaryl group; and

R^5 is selected from $R^{5'}$, halo, $NHR^{5'}$, $C(=O)NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, $NHC(=O)R^{5'}$, $NHC(=O)NHR^{5'}$, $NHS(=O)_2R^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl (optionally substituted by halo, NH_2, OH, SH).

2. The use according to claim 1, wherein the raf kinase inhibited is B-raf kinase.

3. The use of a compound of the formula I:



or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for use in the treatment and/or prophylaxis of cancer, wherein:

-X=Y- is selected from $-CR^2=CR^3-$ and $-CR^2=N-$;

R^1 is selected from H, halo, NRR', NHC(=O)R, NHC(=O)NRR', NH_2SO_2R, and C(=O)NRR', where R and R' are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, SO_2-NH_2, C_{5-20} carboaryl, C_{5-20} heteroaryl and C_{3-20} heterocyclyl, or may together form, with the nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group;

R^2 and R^3 (where present) are independently selected from H, optionally substituted C_{1-7} alkyl, optionally substituted C_{5-20} aryl, optionally substituted C_{3-20} heterocyclyl, halo, amino, amido, hydroxy, ether, thio, thioether, acylamido, ureido and sulfonamino;

R^4 an optionally substituted C_{5-20} carboaryl or C_{5-20} heteroaryl group; and

R^5 is selected from $R^{5'}$, halo, $NHR^{5'}$, $C(=O)NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, $NHC(=O)R^{5'}$, $NHC(=O)NHR^{5'}$, $NHS(=O)_2R^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl (optionally substituted by halo, NH_2, OH, SH).

4. The use according to any one of claims 1 to 3, wherein -X=Y- is $-CR^2=N-$.

5. The use according to any one of claims 1 to 4, wherein R^5 is selected from $R^{5'}$, halo, $NHR^{5'}$, $OR^{5'}$, $SR^{5'}$, wherein $R^{5'}$ is H or C_{1-3} alkyl, optionally substituted by halo, NH_2, OH, SH.

6. The use according to claim 5, wherein R^5 is selected from H and NH_2.

7. The use according to any one of claims 1 to 6, wherein R^1 is selected from H, NRR', NHC(=O)R, NHC(=O)NRR', and NH_2SO_2R.

8. The use according to claim 7, wherein R^1 is selected from H and NH_2.

9. The use according to any one of claims 1 to 8, wherein R^2 is selected from H, halo, amino, hydroxy and thio.

10. The use according to claim 9, wherein R^2 is selected from H and halo.

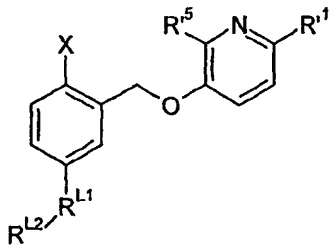
11. The use according to any one of the preceding claims, wherein R^4 is an optionally substituted C_{5-10} aryl group.

12. The use according to claim 11, wherein R^4 is selected from a C_{5-10} carboaryl group and a C_{5-10} heteroaryl group having one or two nitrogen ring atoms.

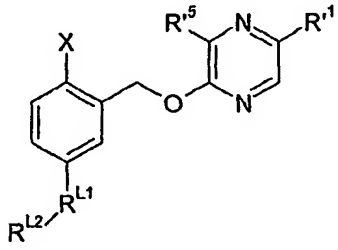
13. The use according to claim 12, wherein R^4 is an optionally substituted phenyl or napthyl group.

14. The use according to claim 13, wherein R^4 is a phenyl group substituted with one or two substituents independently selected from halo, ether, C_{1-7} alkyl, C_{5-20} aryl, amido, acylamido, ureido, carbamate and reverse carbamate.

15. The use according to any one of claims 1 to 3 of a compound of formula **IIa or IIb**:



(IIa)



(IIb)

wherein:

R'^1 is selected from H, $NR^{C1}R^{C2}$, $NHC(=O)R^{C1}$, $NHC(=O)NR^{C1}R^{C2}$, $NH_2SO_2R^{C1}$, and $C(=O)NR^{C1}R^{C2}$, where R^{C1} and R^{C2} are independently selected from H and C_{1-4} alkyl, and are optionally substituted by OH, NH_2, C_{5-20} carboaryl, and C_{5-20} heteroaryl, or may together form, with the

nitrogen atom to which they are attached, an optionally substituted nitrogen containing C_{5-7} heterocyclyl group;
R'^5 is selected from H and NH_2;
X is selected from H and halo;
R^{L1} is selected from -NH-C(=O)-, -NH-C(=O)-NH-, -NH-C(=O)-O- or -O-C(=O)-NH-;
R^{L2} is selected from H, optionally substituted C_{5-20} carboaryl and optionally substituted C_{5-20} heteroaryl, except that R^{L2} cannot be H when R^{L1} is -NH-C(=O)-O-.

16. The use according to claim 15, wherein the compound is of formula **IIa**.

17. The use according to claim 16, wherein
R'^1 is selected from H and $NR^{C1}R^{C2}$.

18. The use according to claim 16, wherein R'^1 is selected from H and NHR^{C1}.

19. The use according to any one of claims 16 to 18, wherein R'^5 is H.

20. The use according to any one of claims 16 to 19, wherein X is halo.

21. The use according to any one of claims 16 to 20, wherein R^{L1} is -NH-C(=O)-.

22. The use according to any one of claims 16 to 21, wherein R^{L2} is a C_{5-20} carboaryl or C_{5-20} heteroaryl group.

23. The use according to claim 15, wherein the compound is of formula **IIb**.

24. The use according to claim 23, wherein
R'^1 is selected from H and $NR^{C1}R^{C2}$.

25. The use according to claim 24, wherein R'^1 is selected from H and NHR^{C1}.

26. The use according to any one of claims 23 to 25, wherein R'^5 is H.

27. The use according to any one of claims 23 to 26, wherein X is halo.

28. The use according to any one of claims 23 to 27, wherein R^{L1} is -NH-C(=O)-.

29. The use according to any one of claims 23 to 28, wherein R^{L2} is a C_{5-20} carboaryl or C_{5-20} heteroaryl group.

30. The use according to any one of the preceding claims wherein the condition treated is a disease or condition with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals; or

(d) upregulation of growth factor receptors, such as ERB2 and EGFR.

31. A method for the treatment of a condition ameliorated by the inhibition of raf kinase comprising administering to a subject suffering from said a condition ameliorated by the inhibition of raf kinase a therapeutically-effective amount of a compound as described in any one of claims 1 to 29.

32. A method for the treatment of a cancer comprising administering to a subject suffering from cancer a therapeutically-effective amount of a compound as described in any one of claims 1 to 29.

33. A method according to either claim 31 or claim 32, wherein the condition treated is a disease or conition with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals;

(d) upregulation of growth factor receptors, such as ERB2 and EGFR.

34. A method for the prevention or treatment of (or alleviating or reducing the incidence of) a disease state or condition characterised by up-regulation of a raf, which method comprises:
(i) subjecting a patient to a diagnostic test to detect a marker characteristic of up-regulation of the raf kinase; and
(ii) where the diagnostic test is indicative of up-regulation of raf kinase, thereafter administering to the patient a compound of the formula (I) as defined in any one of claims 1 to 29 having raf kinase inhibiting activity.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002877

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P35/00 A61K31/4412 A61K31/4965

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/004720 A (CONGREVE MILES STUART ; FREDERICKSON MARTYN (GB); WOODHEAD ANDREW JAME) 15 January 2004 (2004-01-15) abstract page 8, paragraph 1 claims	1-34
P,X	WO 2004/007472 A (ONO PHARMACEUTICAL CO ; KOKUBO MASAYA (JP); SAGAWA KENJI (JP); SHIBAYA) 22 January 2004 (2004-01-22) abstract examples	1,2, 4-31,33, 34
X	US 5 990 133 A (DAVIES DAVID THOMAS ET AL) 23 November 1999 (1999-11-23) column 1, lines 1,2 examples	1,2, 4-31,33, 34

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2004	03/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002877

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 409 943 A (IFE ROBERT J ET AL) 25 April 1995 (1995-04-25) abstract examples claims	1,2, 4-31,33, 34
A	WANG H-P ET AL: "Preparation and antitumor activities of 'beta!-azatyrosinamides" JOURNAL OF FOOD AND DRUG ANALYSIS 2000 TAIWAN, vol. 8, no. 3, 2000, pages 159-165, XP009038682 ISSN: 1021-9498 the whole document	1-34

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 31-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 1-34 (all in part)

The initial phase of the search of formula (1) in claim 1 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible.

Moreover, the terms "a condition ameliorated by the inhibition of raf kinase" and "a disease or condition characterised by the up-regulation of a raf" (independent claims 1, 31, 34) are no clear definitions of a therapeuc application.

Consequently, the search has been restricted to the use of compounds as in generic formulae IIa and IIb in the treatment of cancer or the specific diseases mentioned on description pages 3 and 8.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB2004/002877

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31-34 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-34 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002877

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